Brain

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BRAIN.

PART I, VOL. 40.

FURTHER OBSERVATIONS ON EXPERIMENTAL TOXI-INFECTION OF THE CENTRAL NERVOUS SYSTEM.[1]

BY DAVID ORR, M.D., AND MAJOR ROWS, R.A.M.C.

THIS communication is a continuation of our experimental work on the action of the bacterial poisons upon the nervous system.

In 1914 [2], after several series of experiments, we drew attention to the differences between lymphogenous and hæmatogenous infection. The first was induced by infecting the ascending lymph-stream of nerves, the second by placing celloidin capsules containing a culture of bacteria in the abdominal cavity. Lymphogenous infection was found to be characterized by:—

(1) Reaction of the cells of the fixed tissues.

(2) Proliferation of the cells of the adventitial sheath of veins and capillaries.

(3) The appearance of scavenger cells to remove disintegrated myelin.

(4) Nerve cell degeneration and neuronophage phenomena.

In hæmatogenous infection we found:—

(1) The nerve cells suffered least of all.

(2) Primary degeneration of the myelin sheath round the cord margin and along the postero-median septum.

(3) Œdema of the cord.

(4) Dilated vessels and hyaline thrombosis.

In brief, lymphogenous infection produces an inflammatory lesion of the central nervous system, while in the hæmatogenous variety inflammation is reduced to a minimum.

We drew attention to the implication of the sympathetic system in the abdominal operations, but did little more than hint at its rôle in the

[1] This research has been carried on with the aid of a grant from the Board of Control.

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causation of the cord lesions. At that stage certain conclusions were drawn, viz., that general paralysis and tabes dorsalis were lymphogenous infections; and that the non-systemic degenerative lesions found in cancer cachexia, pernicious anæmia, and Addison's disease, came under the heading of hæmatogenous infections.

In the above experiments the results of toxic action were studied in the spinal cord only; in the present series the research has been directed towards the brain, and the capsule containing a culture of the *Staphylococcus aureus* was placed in contact with the common carotid artery in the neck. The experiments, though limited in number, have given positive results so far, and are worthy of record, as they help to explain the pathogenesis of certain obscure lesions of the central nervous system found in man. Hyaline thrombosis was found to be a constant result in the cords examined when the capsules were placed in the abdominal cavity, and we find the same morbid change in the vessels of the brain when the capsule is placed against the carotid sheath. The lesions to be described are the direct result of this thrombotic change, and vary in kind with the degree to which the local vascular supply is interfered with.

Rabbits were used for experiment. We have examined three brains so far and have observed two types of lesion.

(1) Coagulation necrosis of the nerve cells in the cornu ammonis, in the cerebral cortex, and in the amygdaloid nucleus.

(2) Softening in the stratum moleculare of the cornu ammonis.

Before entering upon a description of the lesions in the cornu ammonis, let us look for a moment at the structure of this organ. The cornu ammonis of the rabbit consists of, from without inwards, the alveus, the stratum moleculare, the lamina ganglionaris, which here directly concerns us and is composed of pyramidal cells, the stratum radiatum, and most internal of all the lamina involuta whose tangential fibres surround folia of the pia-arachnoid invaginated from the mesial surface of the cerebral cortex.

In one case an area of about one-sixth of the circumference of the lamina ganglionaris showed a considerable degree of coagulation necrosis of the pyramidal cells. In frontal sections, stained by toluidin blue, the cells of the lamina ganglionaris are densely packed together. Normally each shows a thin cell body prolonged into an apical dendrite which projects into the stratum radiatum. The nucleus is relatively very large, is clear, round, or slightly oval: it possesses a nucleolus and two or three particles of chromatin. The chromophile material of

the cell body is in an amorphous condition; the apical process stains exceedingly faintly and is perceptible in the stratum radiatum for a short distance only. The area of the ganglionic lamina affected by coagulation necrosis stands out in marked relief owing to the strong affinity for the aniline dye possessed by the degenerated nerve cells. This area is sharply marked off from, and is appreciably narrower than, the normal portion of either side. Even with a low power the distortion of the altered cells is perceptible, and the sharp definition of the degenerated zone is strongly suggestive of local vascular occlusion. With higher magnification the nerve cell body and nucleus are seen to

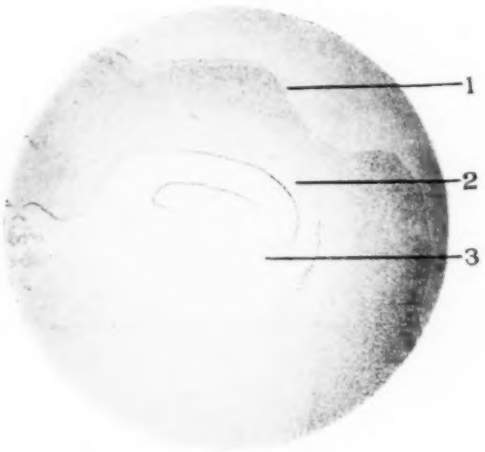

FIG. 1.—Photomicrograph of frontal section through brain of rabbit. Stained by toluidin blue. 1, Cortex cerebri; 2, ganglionic layer of cornu ammonis; 3, fimbria fornicis. The higher power photographs are taken in areas 2 and 3.

be deeply and diffusely stained; both are shrunken and much distorted. The axis-cylinder, which normally is scarcely distinguishable, can be followed into the molecular layer, in which it is seen to give off numerous branches. The apical protoplasmic dendrite is quite prominent, is stained diffusely, at times slightly granular in appearance, and pursues a tortuous course into the stratum radiatum. These alterations are typical of the condition known as coagulation necrosis (fig. 2).

With Van Gieson's method the degenerated area is very distinct. Normally the nerve cell nucleus stains a violet colour by this method

and is clear. In the affected cells the structure of the nucleus can no longer be seen and the degenerated shrunken cell body is yellow in the centre, while its edge is of a reddish orange colour. The tortuous apical process stains in a similar fashion and can be followed for a considerable distance into the stratum radiatum.

In another case two small areas of coagulation necrosis were observed in the cornu ammonis, one at the inner and one at the outer pole. The morbid area at the inner pole of the cornu ammonis was larger than at the outer, and not so extensive as in the experiment described above.

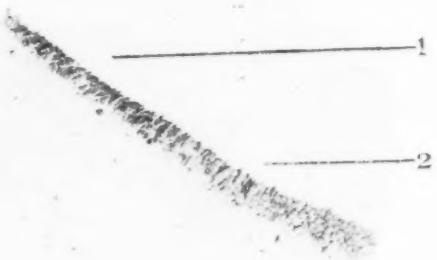

FIG. 2.—High-power view of lamina ganglionaris of cornu ammonis. Toluidin blue. 1, Note the shrinkage and diffuse staining of the nerve cells; 2, junction of morbid with normal area, in which the clear nucleus of the healthy nerve cells is prominent.

By toluidin blue staining there is no shrinkage of the ganglionic lamina in the areas affected and the nerve cells are not quite so distorted as in the previous case. Both cytoplasm and nucleus stain very diffusely. By Van Gieson's method they stain a diffuse orange yellow and stand out sharply from the normal cells of the lamina. The centre of the cell, i.e., the area occupied by the nucleus, is a deeper yellow than the periphery.

The second type of lesion, ischæmic softening, was met with in one experiment, and consists in the softening proper plus the accompanying secondary inflammatory phenomena, the result of the irritative effects of

degenerative products on the surrounding tissues, and in the reaction incidental to repair. The softening proper is situated in the stratum moleculare; it just touches the lamina ganglionaris on the one side and the fornix on the other (fig. 3). It consists in layers which can be differentiated into four for purposes of description. The first, in the centre, is composed of detritus amongst which can be seen altered red blood corpuscles, fragments of nuclei deeply stained, and some clear faintly stained distorted oval nuclei. Immediately outside this area is a narrow band of round deeply stained nuclei, some of which are surrounded by a small quantity of protoplasm. These are loosely

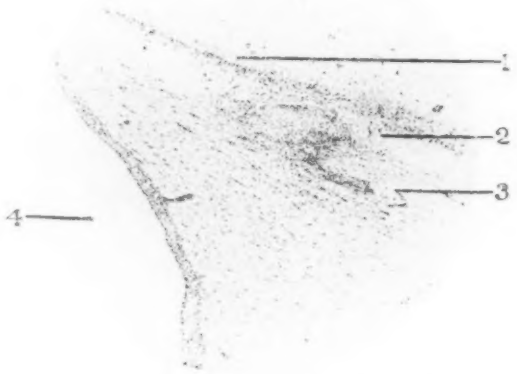

FIG. 3.—1, Lamina ganglionaris of cornu ammonis; 2, area of ischæmic softening; 3, vessel showing periarteritis; 4, lateral ventricle.

arranged, and amongst them lie many granular epithelioid cells. The third layer of epithelioid cells or compound granular corpuscles is not sharply marked off from the second of small round cells, and is a dense layer. These epithelioid cells possess a large cell body of varying shape—the result of pressure—which is finely fenestrated, and the nucleus, almost invariably of medium size, is round or oval, and clear. A large number of epithelioid cells show vacuolation, and it is worthy of note that in a very small number only the nucleus is of the small, dark, shrunken, and excentrically placed type so characteristic of the scavenger cell in softenings of long standing. Outside the area of scavenger cells the inflammatory phenomena consist in small round

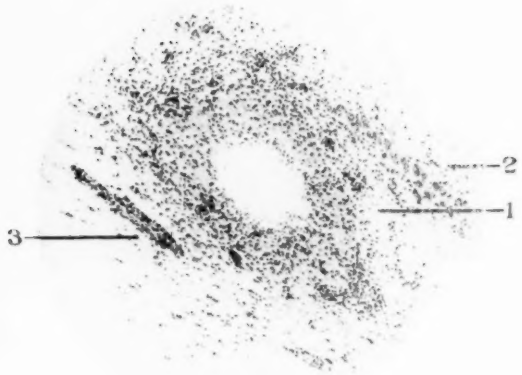

FIG. 4.—1, Area of softening under higher magnification; the central necrotic zone is surrounded by compound granular corpuscles and small round cells; 2, nerve cells of lamina ganglionaris; 3, periarteritis.

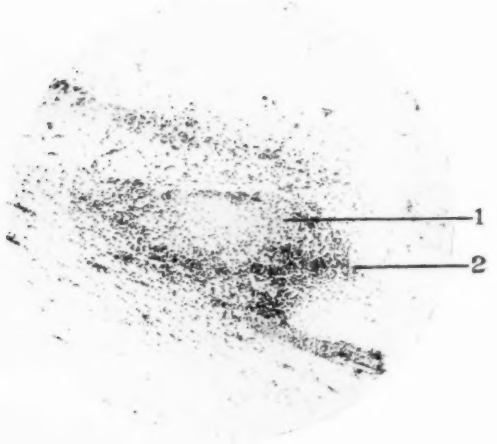

FIG. 5.—To show: 1, the compound granular corpuscles surrounded by 2, small round cells.

cells, reaction on the part of the neuroglia, and in proliferation of the adventitial cells of the neighbouring vessels (figs. 4 and 5).

The small round cells lie free in the tissue and possess a rounded or oval nucleus deeply stained and filled with chromatin. The cytoplasm is finely granular and varies considerably in quantity. In some it forms a very narrow band round the nucleus, in others it is in greater quantity, placed for the most part to one side of the nucleus and is vacuolated. These features are found in the plasma cell in the early phases of its development.

The neuroglia participates actively in the inflammatory reaction and round the area of softening there is much neuroglial proliferation and hypertrophy. In those cells undergoing active hypertrophy the nucleus is enlarged, round or oval, and clear; the cytoplasm is greatly increased in quantity, is vaguely granular, stains more deeply at its edge, and is prolonged into short thick processes. This is the amœboid type, and between this and the normal are many pre-amœboid stages. Lying amongst the above are cells with an oval, pale nucleus situated at one extremity of a large protoplasmic body. There are others somewhat similar in type to these, in which the body is more fusiform. Both varieties resemble young fibroblasts very closely. Many neuroglia cells are in a degenerative phase; the cytoplasm is disintegrating and the nucleus has undergone shrinkage and stains diffusely. In another type of glia cell, found at the periphery of the softening, the nucleus is small, dark, and usually rounded, though in some instances it is slender. The cytoplasm streams away from either end of the nucleus in a thin elongated process which is not uncommonly branched, when the cell is quite indistinguishable from the "Stäbchenzell" so frequently found in certain inflammatory conditions, and acknowledged to be a derivative of the neuroglia or adventitial cells, though for the most part from the former.

There is a high degree of proliferation of the adventitia of the small vessels in the immediate vicinity of the softening. The adventitial nucleus has become rounded, reduced in size, rich in chromatin and surrounded by a finely granular protoplasmic body. The adventitial sheath is packed with young plasma cells similar to those lying free in the surrounding tissues. The small venules and capillaries at a little distance from this softened area show a lesser degree of adventitial proliferation. This reaction can be followed inwards as far as the median portion of the fornix, laterally amongst the venules of the lateral ventricles, and affects in a marked degree the small vessels in

the stratum radiatum and the lamina involuta, which form the inner parts of the cornu ammonis.

In the cerebral cortex there are no gross lesions such as the ischæmic softening in the cornu ammonis, but the nerve cells exhibit varying degrees of coagulation necrosis. A description of this morbid change has been already given in the case of the ganglionic layer of the cornu ammonis. The cortical cells show precisely the same morbid features and staining reactions so characteristic of this type of affection. The coagulation necrosis is not distributed in a uniform manner throughout the cortex in each experiment. Sometimes the upper and lateral regions may contain the degenerated cells, while the mesial, insular and under surfaces are quite normal or practically so. On the other hand the morbid change may involve the mesial, upper, lateral and under surfaces of the cerebellum, thus embracing the pallium and rhinencephalon. When the olfactory lobe shares in the necrotic change its necrosed cells show up very prominently owing to the sharp contrast between the ganglionic layer and its covering clear molecular lamina.

In the superior and lateral areas of the pallium the morbid change varies in degree from point to point, contiguous territories showing slight variations in intensity; and all the cortical cell laminæ are not involved in the necrotic change. For our present description we may divide the cortex into, from without inwards: (1) The molecular zone; (2) the external granular zone; (3) pyramidal layer; (4) internal granular zone; (5) ganglionic layer; (6) multiform layer. All these zones are not always distinct or present; certain variations in cell lamination occur in different portions of the cortical field, but the layers as given above serve our present purpose.

The whole depth of the grey matter does not exhibit coagulation necrosis of the nerve cells. The morbid change includes all the outer layers as far inwards as the ganglionic lamina: it is rare to find morbid nerve cells in the deepest or multiform layer. In the outer layers the degenerated nerve cells may be very numerous or in fewer numbers according as one passes from one point to another, and granule and pyramidal cells are affected indiscriminately.

So far we have not met with any proliferative changes in the neuroglia of the cortex, either in the molecular zone or elsewhere, but in the capillary walls there is evidence of an early reaction shown by the hyperchromatism and rounding of the wall nuclei. The vessels throughout the brain are dilated, congested, and are the seat of hyaline thrombotic changes, to which further reference will be made.

In addition to the cortical areas above referred to there are two other regions whose cells are necrotic, and one, the cornu ammonis, has already been dealt with. But there is another, the amygdaloid nucleus, whose cells show as intense a degree of morbid change as in any of the areas already described. The amygdaloid nucleus is situated in the anterior portion of the temporal lobe. Its lower part joins with the tail of the caudate nucleus. Superiorly it is carried into the putamen of the lenticular nucleus, while anteriorly it is continuous with the temporal grey cortex. In the sections under description, it appears as an elongated oval beneath the basal ganglia, and its cells show the shrinkage and diffuse staining so characteristic of coagulation necrosis, throwing the entire nucleus into sharp contrast with the surrounding parts. It is perhaps not without significance that in the experiment, in which this nucleus was affected, the cornu ammonis of the same side showed a definite band of coagulation necrosis in the ganglionic layer. Still, for the present one would hesitate in the absence of more extensive observation and confirmation to lay stress upon what may be a coincidence.

The areas which show lesions in these experiments are the cortex of the pallium and rhinencephalon, the cornu ammonis, and the amygdaloid nucleus. In the cornu ammonis there are two distinct zones affected, and in each the pathological lesion is widely different in type. In the one, where the ganglionic layer is the seat of the lesion, the cells show coagulation necrosis, precisely the same variety of morbid change exhibited by the cells of the cerebral cortex and the amygdaloid nucleus; on the other hand, where the white matter of the cornu ammonis is involved, i.e., in the stratum moleculare, the lesion is of a totally different nature. Here a localized ischæmic necrosis has occurred with all the hæmorrhagic and inflammatory phenomena peculiar to a thrombotic infarct.

It is of importance to note that the above areas and no other are the seat of morbid changes, and that they are supplied by cortical vessels derived from the pia-arachnoid. This is obvious in so far as the pallial and olfactory cortices are concerned, but at first sight not quite so apparent in regard to the cornu ammonis and amygdaloid nucleus. We know, however, that the central portion of the cornu ammonis—the lamina involuta—is penetrated by folia of the pia-arachnoid accompanied by vessels; while the amygdaloid nucleus is continuous with the grey matter of the temporal lobe. The affected areas therefore all possess one important point in common, i.e., their blood-vessels are

derived from the pial system, a fact which explains the participation of the above-mentioned nuclei in the morbid process.

The lesions in the brain agree anatomically with what was observed in the spinal cord in an earlier series of experiments on animals, when after the abdominal cavity had been infected by toxins the myelin was found degenerated round the margin of the cord and on either side of the postero-median septum, while the central portions including the grey matter remained intact. Here again the degenerated elements lay within the zone of pial supply and had suffered exclusively. If we substitute grey for white matter in the two series of experiments the anatomical distribution of the morbid lesion is essentially similar, i.e., the peripheral portions of the central nervous system subserved by branches from the pial vascular system are affected.

The morphological character of the lesions in the brain point very clearly to a disturbance of the circulation and therefore of nutrition. This, in the cerebral cortex, affects a wide area and finds its expression in the necrosis of nerve cells in all laminæ except the deep multiform layer, unaccompanied however by any local ischæmia indicative of complete vessel blockage. The evidence of a much more severe local nutritional disturbance is very obvious in the ganglionic and molecular layers of the cornu ammonis, where in the former a short segment of nerve cells is necrosed and sharply defined from the normal cells on either side, and in the latter where a necrotic softening with all the histological phenomena incidental to an infarction have occurred. The cause of the disturbance of the circulation is to be found in the morbid condition of the cerebral vessels, which are dilated, engorged, and show many varieties and degrees of hyaline degeneration of their contents.

In some vessels the corpuscles are normal or nearly so, but the majority show hyaline changes; and as a result of this, hyaline thrombosis has occurred which is recognizable in its various stages from the early, where the vessel is still permeable, to the late, where occlusion becomes inevitable. Arteries, veins, and capillaries are affected, and the thrombotic change, accompanied by dilatation of the perivascular and pericellular spaces due to œdema, is found in the vessels of the pia-arachnoid, the grey, and the white matter. All elements of the blood participate in the thrombotic process. In incomplete thrombosis the hyaline material, in longitudinal section, is seen lying along the side of the intima as two bands of varying density, each of which connects with the other by trabeculæ, so forming a network in the lumen of the

vessel. Within this network are many red corpuscles obviously hyaline, and these at times clump together to form a homogeneous mass. The leucocytes also undergo hyaline degeneration. Their affinity for acid fuchsine is intensified, they lose their normal shape, become clumped into masses in which lie numerous granules deeply stained with hæmatoxylin, and at times arranged in a fashion suggestive of a horse-shoe. We regard these granules as the remains of degenerate leucocyte nuclei. There are many hyaline threads in the vessel lumen to which the leucocytes contribute frequently, forming a hyaline syncytium. Purely fibrinous thrombi are not infrequently observed.

We have frequently observed these hyaline changes in our experiments upon the spinal cord. They are evidence of toxic action upon the blood elements. We find them also in man in cases of acute colitis, and their presence has been noted by others in measles, influenza, diphtheria, typhoid fever, malaria, pneumonia, and pyogenic infection. We have noted this type of vascular lesion also, and its effects, in the cervical enlargement of the cord in a case of cancer of the head of the pancreas. Here the resultant ischæmic softenings, situated in the posterior columns, had been followed by an acute ascending degeneration of the sensory fibres, which we traced segment by segment into the nucleus cuneatus and nucleus gracilis of the medulla. This observation in a clinical case confirmed by our experiments upon the rabbit's brain proves the ante-mortem genesis of the changes in the vessels.

Reference has been made already to the effects of disturbances in the circulation and of nutrition upon the nervous elements, and attention has been directed to the different character of the lesions in the cerebral cortex and the cornu ammonis. Before attempting an explanation of this difference we must in the first place look at some points in connection with the vascular supply of the brain.

A concise statement in reference to this subject will be found in an article on hæmorrhagic encephalitis by Bignami and Nazari [1], in which many important points are mentioned having a direct bearing upon our research. These authors have found that the lesions in the white and grey matter in hæmorrhagic encephalitis differ very materially, and their views regarding the cerebral circulation are based upon this. A sharp distinction is drawn between miliary hæmorrhages, which are characterized by their ring-like form around a necrotic focus and by their situation in the white matter, and the hæmorrhagic infiltration which follows thrombosis of the cerebral sinuses or meningeal veins. The hæmorrhage in this latter condition is extensive, affects the grey cortex, and decreases from without inwards. There are no necrotic foci surrounded by a ring

of hæmorrhage such as occur in the white matter. According to the opinion of the authors both conditions are caused by a local disturbance of the circulation and not by an inflammatory process. In the one case the thrombosis of the cerebral veins induces hæmorrhage in the cortex from stasis; in the other, blockage of a precapillary arteriole results in a circumscribed necrosis in the white matter followed by hæmorrhage in the immediately surrounding parts from the collateral vessels, the pathogenetic mechanism here being precisely the same as in infarction of other organs. If a similar lesion is not produced in the grey matter, through occlusion of the arterioles, it seems more than likely that there is some difference between the circulation in the cortex and the medullary substance. These observations incline the above-mentioned authors to the admission that, although the precapillary arterioles in the white matter are physiologically terminal, those in the grey cortex are not so. In the white matter occlusion of an arteriole is followed by infarction; if this does not occur in the grey matter, evidently then we must admit the possibility of an anastomosis which is functionally adequate.

Many questions regarding the cerebral circulation are still only partially solved or remain obscure, but we are now in possession of certain facts which bear on the subject before us. All are agreed that the cortical arteries do not communicate with the basal arteries. Duret regards the cortical arteries as terminal, but Cordiat and Féré do not agree with this, although they grant that anastomosis is not sufficient to permit of re-establishment of the circulation when obstructed by thrombus or embolus. Heubner supports the view that numerous anastomoses occur amongst the pial arteries, but adds that after their branches have penetrated the cortex anastomosis ceases. On this latter point he is supported by Duret and Beevor, who hold that the cortical arteries are terminal: but, in spite of these definite statements, it would appear that the whole question is worthy of further study since it has been shown that the myocardial arteries are not completely terminal in the anatomical sense, as has hitherto been held.

Of great importance in the field of pathogenesis is a knowledge of the relationship between the short cortical and the long subcortical arterioles. Both are derived from pial arteries. The short are purely cortical, while the long pass straight down into the white matter, where each supplies a very narrow territory owing to the small number of branches given off. Cortical arteries divide at once and very frequently, forming a fine capillary network which is richest in the deepest cortical lamina. Further it appears that the short cortical arterioles anastomose in the depth of the grey matter with the long or medullary branches.

The important point to be specially noted, however, at this stage of our knowledge, is that the cortical vascular network is far richer than that of the white matter.

Whatever our present knowledge may be, from the anatomical side, of the ultimate distribution and connections of the cerebral vascular system, we seem to be justified in assuming from morbid lesions that there is a difference in the two systems which subserve the grey and white matter respectively. The evidence of this is seen in the histological difference between the cortical and subcortical lesions. The former are diffuse and consist in necrosis of the nerve-cell units; the latter—in the cornu ammonis—involve a circumscribed locality and are typical of infarction. As the arterioles, which supply the cortex and the adjacent subcortical zone, have a common origin—the pial arteries—and both systems are affected by toxic hyaline thrombosis in these experiments, the difference in type of the resultant lesions must depend upon the anatomical arrangements of fine capillary branches. The definite restriction of the subcortical lesion with its patho-histological elements can only be interpreted as ischæmic in origin, and secondary to blockage of a terminal artery. But the pathogenetic mechanism of the diffuse coagulation necrosis of the cortical nerve cells presents a more complex problem and is very far from clear. From the character of this lesion we can say definitely that no infarction has occurred, and therefore the presumption might be advanced that cortical arterioles are not terminal. The highest elements, the individual nerve units, alone have suffered, and in a manner which points to interference with their nutrition: but the histological picture is far from what one associates with an ischæmia, and rather suggests a stasis due to blockage of veins, a deficiency of nutriment from narrowing of the lumen of arterioles and capillaries, or both combined, as is most probable. It is only some anatomical factor within the cortex itself which could explain this different type of lesion, and for the present one would be inclined to ascribe importance to the richness of the cortical vascular network, which may counterbalance the effects of mechanical interference with the vascular supply. This seems to us the most reasonable view to take of a question which is still controversial and stands in need of much special investigation.

In the above observations we have two types of lesion which illustrate how the two factors, degree and situation, can produce dissimilar pathological results, although the pathogenesis is the same; and, if we apply this to clinical neurology, it becomes apparent that certain nervous syndromes, though widely different in symptomatology, are patho-

genetically one and the same disease. The difference in symptomatology is in large measure due to the anatomical site of the lesion; but the degree to which the nerve structures are involved is an equally important factor. These points are well illustrated by the implication of part of the pyramidal layer only of the cornu ammonis on the one hand, and a definite softening in its molecular layer on the other. Both varieties of morbid change are the result of blockage of vessels by hyaline thrombosis, and the picture to which this gives rise depends in the first place upon the distribution and calibre of the vessel implicated, and varies with the time which elapses between the onset of the lesion and its examination.

One of the practical applications of these experiments is that they throw light upon the genesis of those infantile cerebropathies which are now regarded as the result of toxi-infections of medium or even slight intensity, contracted as a rule between the fifth and eighth month of fœtal life, or in early infancy. Infantile cerebropathies vary in range from aberrations in type of gyri or sulci to absence of the corpus callosum—sometimes accompanied by absence of the fornix—and on to such gross lesions as porencephaly or even absence of one hemisphere. Evidence of antecedent inflammation and vessel occlusion are found in the brain with both naked-eye and microscopic examination, and the degree of interference with development and the resulting mental deficiency depend upon the extent of the lesion and the functional importance of the nervous tissues involved. Our later experiments can be closely correlated therefore with what is known at present of the pathogenesis of many forms of mental deficiency, and show how toxic hyaline thrombosis of capillaries or even larger vessels can contribute very largely in the production of nervous lesions of different degree.

The precise mechanism of production of the thrombosis is still obscure. Whether it is produced directly by the toxins spreading along the vessel sheaths, or more indirectly through a general intoxication, must remain for the present an open question; and as all vascular phenomena are closely connected with the sympathetic mechanism this must come under examination in future experiments.

We are indebted to Dr. J. L. Stephenson, of Whittingham Asylum, for the photographs accompanying this paper.

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DISSOCIATION OF VISUAL PERCEPTIONS DUE TO OCCIPITAL INJURIES, WITH ESPECIAL REFERENCE TO APPRECIATION OF MOVEMENT.[1]

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CHAPTER I.—INTRODUCTORY.

THE intention of this paper is to show, from the records of cases of visual defects due to injury of the occipital region of the cerebrum, that:—

(1) Movement may be recognized as a special visual perception.

(2) Appreciation of movement returns before the object as such is recognized, if recovery of vision is occurring.

(3) Recovery of vision for movement begins in the peripheral field.

(4) Charts of the fields for appreciation of movement are valuable in prognosis.

(5) The dissociations of visual perceptions are analogous to those found in disturbances of somatic sensibility in cases of cerebral injury, which have been so ably studied by Head and Holmes [3].

Certain of the cases bear incidentally on the question of the cortical representation of the macula, and one indeed also on the cortical representation of the peripheral zones of the retina.

Visual defects are considered from the point of view of vision as a part of general sensation rather than a special sense; and I hope that my results will demonstrate that the elementary visual perceptions, of light, of movement, and of an object, are dissociated in a manner similar to the dissociation which is known to occur when sensory paths conducting primary somatic sensory impressions of touch, of pain, of temperature are interrupted. Moreover, the higher and more evolved

[1] Being a thesis presented for the degree of M.D. (Univ. Aberd.).

visual functions concerned with the spatial orientation of objects *seen* may be affected, with the result that symptoms of faulty projection, comparable with the defects known to result from sensory cortical destruction in spatial orientation of things *felt*, are produced. My results lead me to believe that were cerebral disturbances of the other "special" senses investigated, they too would be found to show a close similarity to those of general somatic sensation.

That the perceptions of light, of form, and of colour, are to be found dissociated when the visual area is injured, has long been known. It has also been recorded that coarse or even fine movements of the fingers may be detected before the fingers presented in the so-called blind field can be recognized. In certain cases of transient hemianopia, Wilfred Harris [2] found that movement was perceived before the test object could be recognized as such; and, indeed, he observed this dissociation in patients in whom the lesions were gross and recovery partial. But, so far as I know, hitherto the fields for movement have not been systematically charted, nor has an attempt been made to inquire into visual dissociations in the light of recent additions to our knowledge of cerebral disturbances of somatic sensation.

The frequency with which patients showing restricted visual fields from occipital wounds declared that they could see nothing when an object presented in the "blind" field was kept stationary, whilst they were immediately conscious of "something" moving when the object was oscillated, suggested that it might be instructive to investigate the fields both for movement and for a stationary object; and if possible to record them separately on the charts. Three methods of examination were employed:—

(1) The rough finger test. This was used in the ordinary way for preliminary examination. In Case 5, where vision recovered in only a limited part of the peripheral field, it was the only method adopted as the patient was unable to fix.

(2) The McHardy perimeter method.

(3) The Bjerrum screen method.

I was able to check the results obtained with the perimeter by the Bjerrum screen in a few only of the later cases.

Description of methods 2 and 3:—

The disk on the slide or on the pointer approached from the periphery, and as soon as the patient said he saw "something" moving, the chart or the screen was marked. If the disk itself was not distinguished at the same point, it was brought nearer the fixation

point till it could be clearly seen, when a record was again made on the chart or screen.

A 1-cm. square or circular white disk was used as the test object, but I have satisfied myself by examining with black and with white disks up to 15 cm. in diameter that, in the class of lesion with which we are dealing here, the same dissociations and practically the same fields are got whatever the size of the test object may be, and whether it be black or white, used against a black background. In this paper by the appreciation of a stationary object I mean the appreciation of a stationary something in the visual field without any accompanying recognition of its shape. Sometimes the recognition of shape was simultaneous with appreciation of the mere presence of the stationary object. The results here were variable, and show that waywardness that is typical of cortical defects on the sensory side. In the following cases those in which the evidence pointed strongly to a cortical lesion showed this waywardness much more constantly than those which were more definitely subcortical. The lack of uniformity and apparent untrustworthiness of the patient in appreciating the shape of the object in a part of the field at one time and not at another, in view of the physiological level of the injury, was very suggestive.

The patients have great difficulty in describing the nature of the movement that they see: it is so vague and shadowy. But they are quite sure that neither shape nor colour can be attributed to it, and that it can be detected in a field which is entirely blind to stationary objects.

Though in the charts that follow the respective fields appear to be sharply marked off one from another, this is not strictly the case. There is no doubt that an area of variable size exists in which the perception of one stimulus merges into that of the other. The outlines of the fields indicate the points at which the patient was definitely conscious of the respective stimuli.

Notwithstanding the admitted crudeness of the perimetric method, especially for the accurate recording of scotomata, I hope that the charts will demonstrate fairly well the point I will try to prove. Where the Bjerrum screen was used to check the results, they were fully corroborated.

Chapter II.—Dissociation between Appreciation of Movement and Recognition of the Object.

In this series of ten cases, nine show the dissociation in the affected field, and one does not. They fall naturally into three groups.

Group 1.—Showing only Perception of Movement in the Affected Field, in Addition to some Perception of Light.

Case 1.—Lieut.-Col. T. was wounded on April 6, 1916, by a bullet in the right occipital region, while advancing into action with his men. He did not fall, and though dazed he carried on. He noticed nothing wrong with his vision at the time. About a quarter of an hour after he apparently lost consciousness, for he remembers nothing further till he found himself in the Rawal Pindi General Hospital, Amara, eleven days after he was wounded. He had been trephined, and the bullet removed.

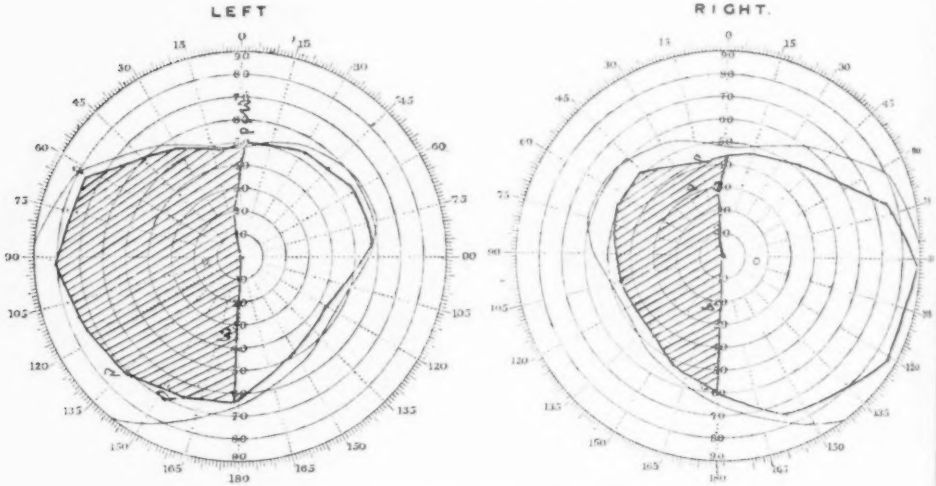


Fig. 1.

It was only when he was transferred to Bombay on May 17 that he noticed he could not see objects on his left. He used to miss pieces of meat on the left side of his plate, but in a good light he could tell if an object were moved in his left half field.

He was evacuated for England on June 6, with no change in his vision, and was admitted to the Empire Hospital on June 29, under the care of Dr. Leonard Guthrie.

On roughly testing his visual fields by the finger test, I found that he quickly perceived finger movements in the whole of the left half field, though when the fingers were kept stationary he saw nothing; and, moreover, that the field for movement compared with my own was normal.

Fig. 1.—Central vision $\frac{6}{6}$, right and left. The fields were mapped out, three months after the date of his injury, with the perimeter (test object, 1 cm. square white disk), and the charts showed a complete homonymous hemianopia, up to the fixation point, for a stationary object, and a full field for movement.

Fields taken one month later showed no alteration, and six and a half months after the injury there was still complete absence of object vision in the left half field.

Striking features of this case are :—

(1) The complete dissociation of the two types of visual stimuli in the left half field.

(2) The full field for movement.

As will be demonstrated by the charts that follow, of cases of hemianopic loss, where appreciation of movement returns, the recovery is never complete, a paracentral or central scotoma remaining as an end-result, to represent the amount of irreparable damage done to the visual area. The nearest approach to a scotoma I could get by repeated examination was a feebler perception of movement in a small part of the upper quadrant about 20° from the fixation point; but the patient declared emphatically that it was never absolutely lost.

(3) The effects of the dissociation on the patient.

This vision for movement alone introduces more difficulties into the ordinary life of the patients than when they are totally blind in the half field. The disparity between the stimuli received from the two halves of the retina is frequently sufficient to affect their equilibrium in walking. They tend usually to sway to the partially blind side, though in the cases I have seen the disability has never been sufficient to make them actually fall. This disturbance is of course most noticeable where the full half field is affected.

Apart from the effect on equilibrium, the inequality of the sensations received by the brain is often a source of considerable annoyance to the patient. In Case 1, for example, the patient, when travelling by train, could see nothing but vague movements on looking out of the windows on his left; but he could read the names of the stations, and

appreciate the scenery from the windows on his right. It is so disconcerting to him that now he thoroughly dislikes train journeys. As he explained, the consciousness of "something moving" kept up a continual desire to turn the head to see what it was, and the gratification of the desire only resulted in annoyance at being tricked again.

The "moving things" have no distinct shape, and the nearest approach to colour that can be attributed to them is a shadowy grey.

Case 2.—Second-Lieut. W. was wounded on February 9, 1916, by a piece of bomb casing, in the occiput. Though he could see from the beginning he knew his sight was affected. He had photophobia, but no abnormal subjective visual sensations. At the Casualty Clearing Station an operation was performed the same day. The Medical Officer there reported that he had a left homonymous hemianopia on admission, and that on February 15 the hemianopia had lessened.

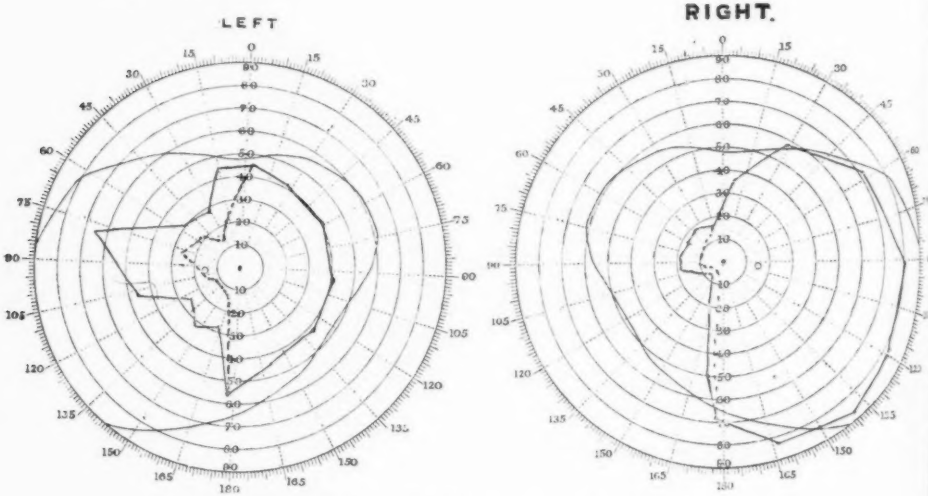
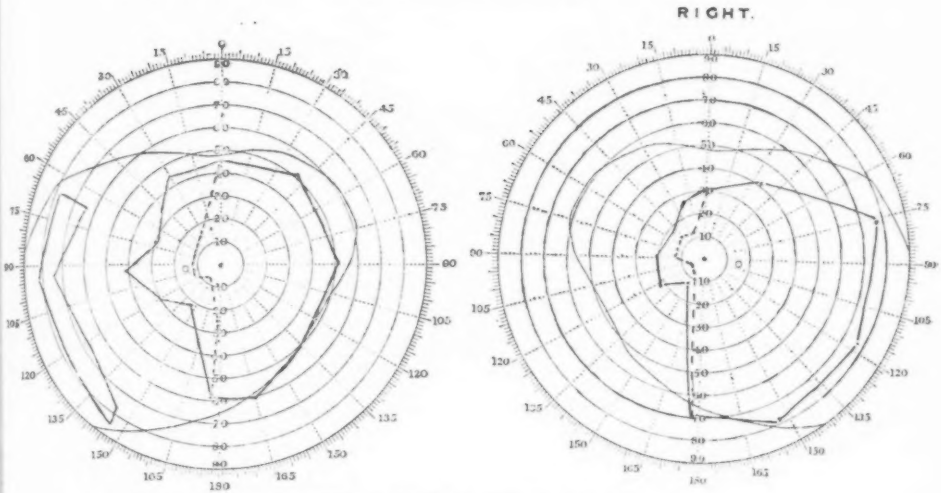


FIG. 2.

Major Austin, at No. 2 Red Cross Hospital, Rouen, noted that optic neuritis was associated with the hemianopia. The loss of vision in the half field was complete on March 12.

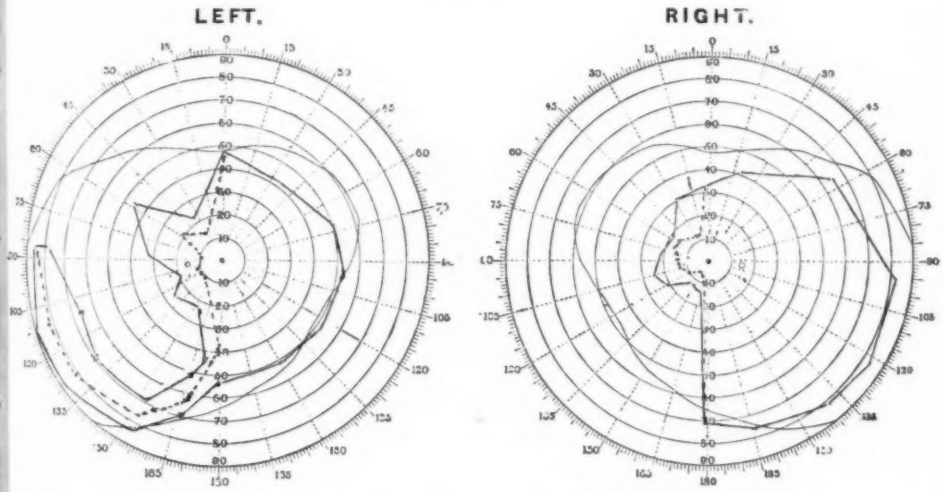
He was admitted to the Empire Hospital on March 17, under the care of Dr. Head, and the following fields were recorded a few days after, and six weeks after the date of the injury.



= Field for movement stimuli.

= Field for object stimuli.

FIG. 3.



= Field for movement stimuli.

= Field for object stimuli.

FIG. 4.

Fig. 2.—Central vision $\frac{6}{60}$ indistinctly right, and $\frac{6}{9}$ left. The fields for the two eyes differ considerably, but in both the perceptions of object and movement are dissociated. The dissimilarity of the two fields made the observer doubt the accuracy of his observations, but a second record made of the fields was very similar. One notes that the dissociation is greatest in the horizontal plane, where most vision is retained.

At the time the next charts were taken, two months later, the patient declared that when he was walking in the street he could see "something moving" for a moment, as people passed him from behind and on his left. He lost it as they got just in front of him, and then it reappeared again as they approached his central vision. The "moving something" had neither form nor colour. It gave him the impression of a shadow.

Fig. 3.—The perimetric charts confirmed this, but showed that only the left eye perceived movement peripherally, practically no change being noted in his right field. Moreover, peripheral vision in the left eye was not complete, being deficient in the upper and lower parts of the left half field.

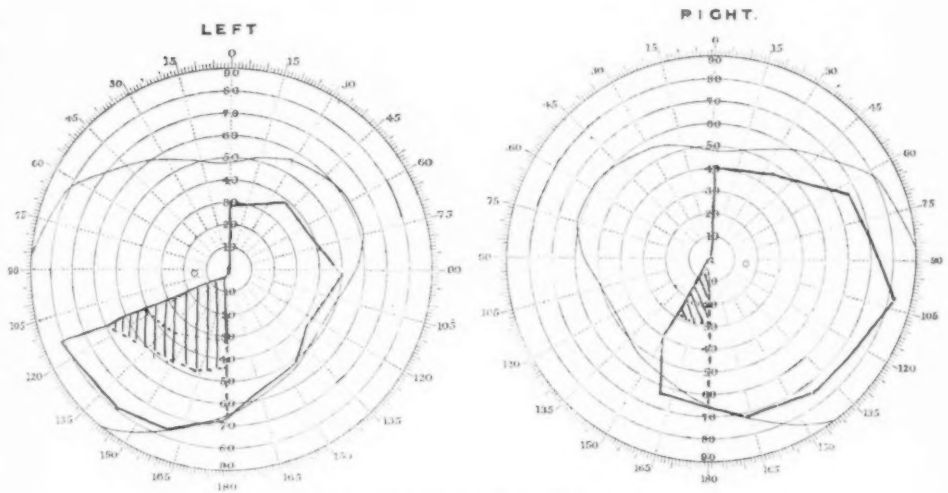
Shortly after this he was discharged to a convalescent home, and then was given sick leave. He reported himself again on December 3 for re-examination, and a record of the fields was taken.

Fig. 4.—Central vision in the right eye had improved, being now almost $\frac{6}{12}$. No alteration had occurred in the field of the right eye. In the field of the left, however, movements were recognized in the periphery of the left lower quadrant, and in the narrow part of the field, outside the dotted line, he saw the white object. The chart showed no appreciable change in the upper quadrant.

On the following day the records of the fields were checked on the Bjerrum screen. Three test objects were used: (1) A circular white disk, 1 cm. in diameter: (2) a circular white disk, 15 cm. in diameter: and (3) a circular black disk, 15 cm. in diameter. The same dissociation of the fields for the two stimuli was got, and practically no change in the size of the respective fields could be demonstrated. So that the size, or the colour (black or white), of the test object make little difference.

Harris [2] records a somewhat similar case of partial hemianopia, in which vision for the white test object was retained in a strip of the peripheral field, and mentions a parallel case of Delépine's [1] of right hemianopia up to the fixation point, with a narrow peripheral zone of vision in the lower right quadrant of the right eye field only.

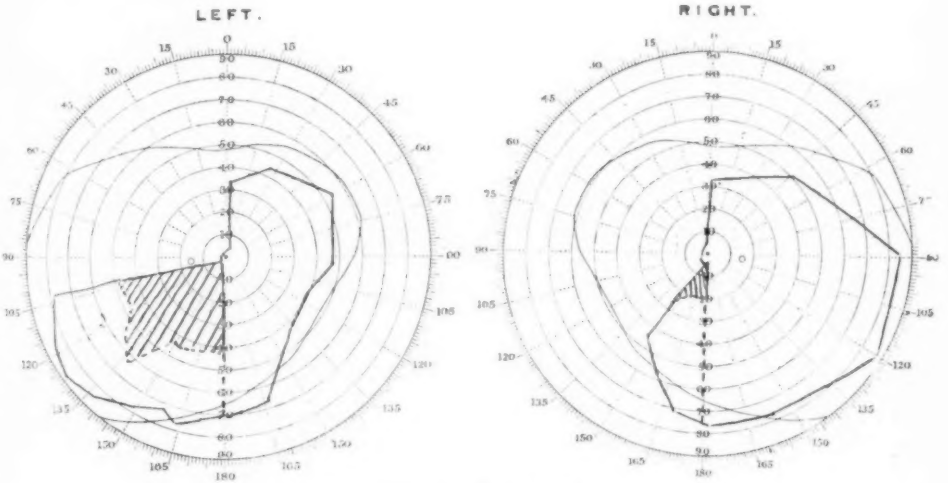
Case 3.—Captain de W. was wounded at Gallipoli on December 4, 1915, by a shrapnel bullet. He never lost consciousness, and he was aware, almost from the first, that he was blind in the left half fields. Though his right leg and arm were weak, he was able to hop to the dressing station.



Object not recognized in left half-field.

= Area in left half field in which movement is appreciated.

FIG. 5.



Object not recognized in left half-field.

= Area in left half-field in which movement is appreciated.

FIG. 6.

The entry wound, in the left frontal region, was enlarged the same night by Mr. Warren Low. There was no exit wound. By X-ray examination the bullet was found to be lying just inside the skull, near the right occipital pole. On January 7 it was removed, and an abscess evacuated.

The fields of the patient were examined at Alexandria by Col. Eason a few days after he was wounded. There was a complete left homonymous hemianopia up to the fixation point. He missed food on the left side of his plate.

To Dr. Farquhar Buzzard, who examined him on May 31, 1916, I am indebted for the following note: "Vision in the left upper quadrant lost. Some return of vision in the left lower quadrant."

The patient had two fits, the first on March 20 and the second on March 30. He was admitted to the Empire Hospital for treatment in the beginning of September under Dr. Buzzard. He gave a history of having been unable, during the earlier months of his illness, to perform purposive movements with his right hand, and a few symptoms of right motor apraxia remained, though it had apparently cleared up to a great extent. He had much less difficulty in knowing what to do with things, but he still had to think about every action. He could not perform movements spontaneously. There was only slight loss of power of sensation in the right arm. There was no agnosia, and he never failed to recognize the use of an object which he saw or felt.

He noticed first some recovery of vision in May, 1916. The movement of objects only was perceived, and solely in the periphery of the lower quadrant. The patient, describing this vision in a small strip of the half field, said that he saw the movement of objects below and to the left momentarily, but only to lose them again as they approached the centre of his field. When walking in the street he could see what he knew must be people's feet, though they had no shape, moving on the left, but he saw nothing to represent the body above the ankles.

Since May he has become aware that the narrow strip has increased in area from the margin towards central vision, and upwards towards the left upper quadrant. He still cannot see stationary objects on his left, even in the lower peripheral fields. The moving things, he says, have a vague grey shadowy appearance.

Fig. 5.—Central vision $\frac{6}{12}$, right and left, nine months after the date of the injury. There is a left upper quadrantic loss, up to the fixation point, for both stimuli; but movement is perceived in the lower part of the periphery of the inferior quadrant. The strip is of larger area in the chart for the left eye. There is still a left homonymous hemianopia for the recognition of an object.

Fig. 6.—Eleven months after the injury: The hemianopic line is seen to miss the fixation point by about 4° or 5°. The movement field in the lower quadrant is now broader and longer, but a paracentral scotoma is still left, and a stationary object is not appreciated in any part of the half field.

The perimetric results of this case have been checked by the Bjerrum screen, and disks black and white up to 15 cm. in diameter were used.

He exhibited certain defects in visual orientation, but these will be described separately in Chapter III.

Case 4.—Capt. C. received a wound at Gallipoli by a shrapnel bullet, in the left occipital region, on June 6, 1915. While advancing he was struck down, stunned but not unconscious. He had no pain, and was able to get up again. At the time he noticed nothing wrong with his vision. As he was walking back to the dressing station he fell down unconscious, and remained so for twelve hours. He was trephined on board the hospital ship that took him to Malta.

I first recorded his fields on September 28, 1915. Though he was at that time quite aware of his loss of vision, which was chiefly in the right upper quadrant, though the lower quadrant was also restricted, it hardly interfered at all with his walking. He had no appreciation of movement, or other visual stimuli, in the blind fields.

Fig. 7.—Central vision $\frac{6}{6}$, right and left. The fields for the recognition of movement and object coincide.

Fig. 8.—The fields were charted again on November 18. There was still no dissociation evident of the fields for the two stimuli. He complained of more difficulty in getting about, that he was more blind. The restriction of the right lower quadrant was found to be greater.

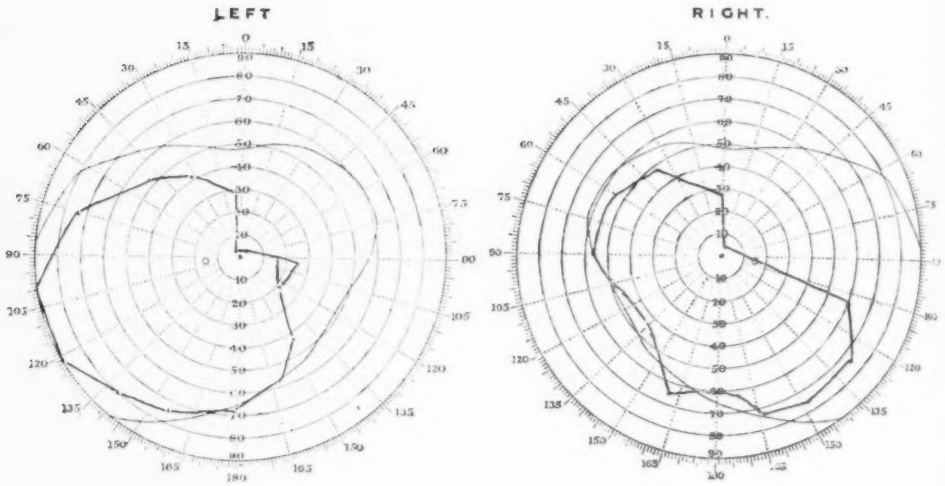
Fig. 9.—The chart dated December 13 (i.e., six months after injury) showed the right lower quadrant field to be a little larger, and at the points marked ×, corresponding to the periphery of the upper blind quadrant, he saw, for a second, the slide moving past.

These points complete the periphery of the right eye field, but correspond, in the chart of the left eye, only to that of the defective part of the right lower quadrant. The patient declared he could distinguish no object as the slide went past, but he knew that something had moved through his blind field. Vision was obviously recovering in the periphery.

On February 1, 1916, he was admitted to the Empire Hospital, for observation, under Dr. Guthrie. Fig. 10 shows his fields for the recognition of movement and object, taken with the perimeter, three days later.

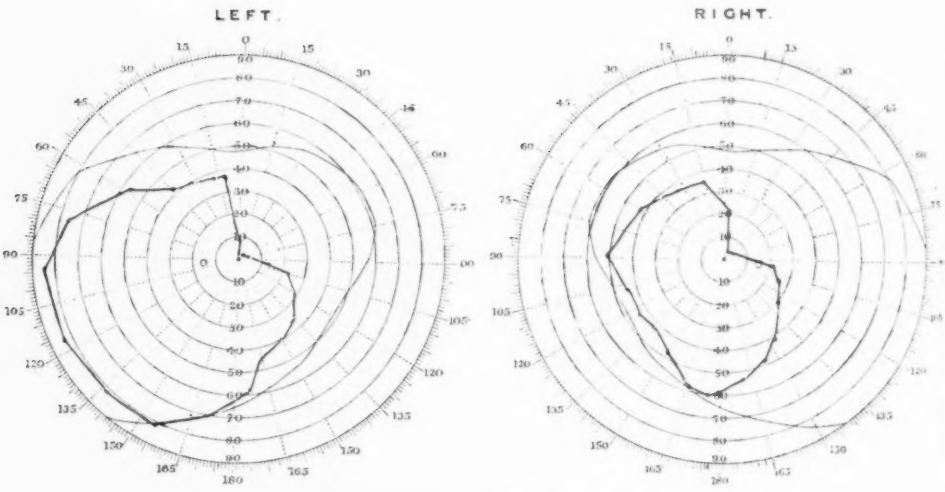
Fig. 10.—Except for a slight restriction of the peripheral parts of the right upper quadrant, more especially in that of the right eye, and a triangular central scotoma for movement in the original blind part of the field, touching the fixation point, the field is complete for movement, and has not changed for the recognition of the object.

The patient was discharged, a few days afterwards, to the country, and no opportunity was got of making a further record till July 10, when he reported himself, complaining that his vision was not quite so good. Fields were then mapped out for object and movement vision.



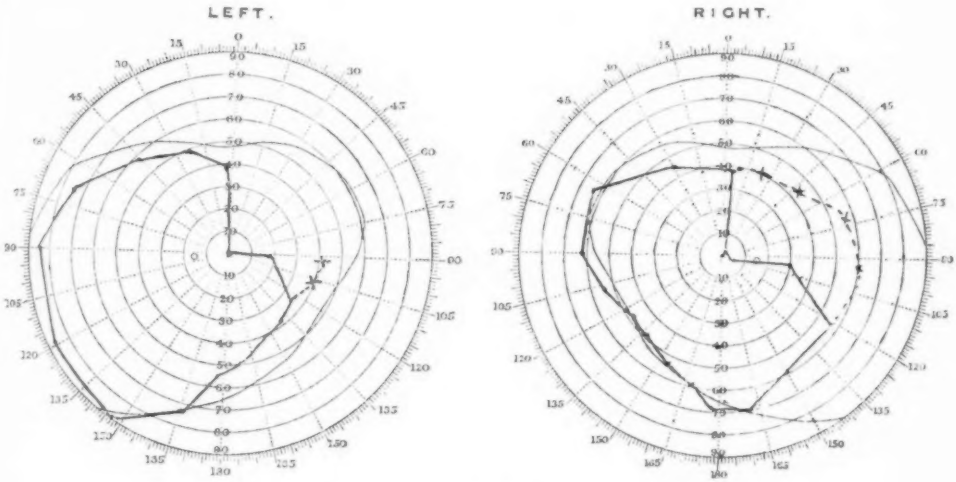
The fields for movement and object coincide.

FIG. 7.



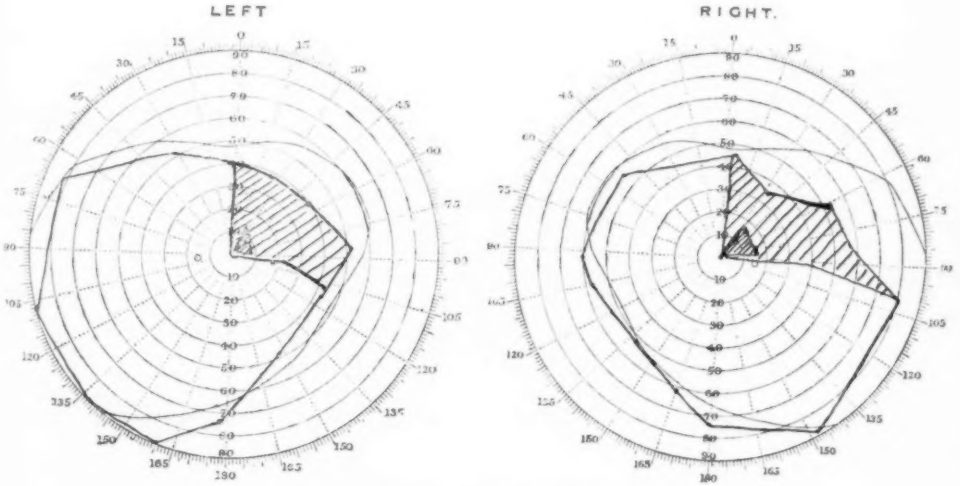
The fields for movement and object coincide.

FIG. 8.



+ + + = Points at which the patient was conscious of movement for a second.

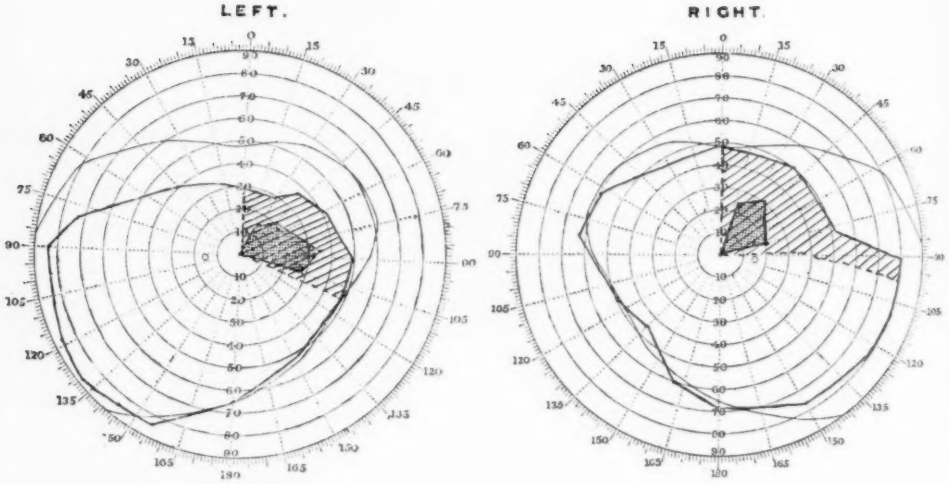
FIG. 9.



▨ = Quadrantic defect for recognition of the object.

▨ = Central scotoma for appreciation of movement.

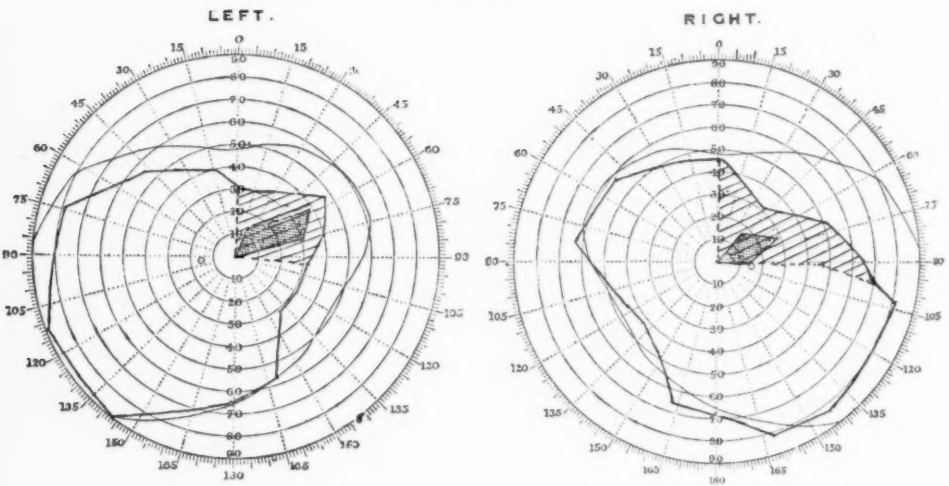
FIG. 10.



= Quadrantic defect for recognition of the object.

= Central scotoma for appreciation of movement.

FIG. 11.



= Quadrantic defect for recognition of the object.

= Central scotoma for appreciation of movement.

FIG. 12.

Fig. 11.—The field for movement has altered little, except that the scotoma is a little larger; and a complete absence of object vision, up to the fixation point, is demonstrated in the right upper quadrant.

Fig. 12.—Recorded thirteen months after he was wounded. There is still no sign of return of object vision in the upper quadrant, and the scotoma for movement has apparently not diminished much.

Prominent features of this case are:—

(1) The return of perception of movement alone.

(2) The recovery occurring in the periphery of the original blind field, leaving as an end result a central scotoma.

(3) The loss of vision going up to the fixation point.

Case 5.—Capt. H. was wounded on December 16, 1915, by shrapnel in the occiput. Dazed but not unconscious, he realized he was completely blind. They carried him back to the field dressing station, where his wound was attended to. The medical officer at No. 2 Casualty Clearing Station reported that he was admitted there the same night with a serious gunshot wound of the vault, which was bleeding freely. He was unconscious, and in a critical state. The following day the wound was cleaned, and some fragments of bone, which were found to be damming a torn longitudinal sinus, were removed.

On January 10 he was transferred to No. 1 Red Cross Hospital, Le Touquet, for better nursing and comfort. The first note made on vision was dated January 28: "? Very slight vision right eye. Blurring of left disk."

On admission to the Empire Hospital on February 26, under the care of Dr. Buzzard, he was very confused and moaned continually. He had some paralysis of the right face, arm and leg, and there was a large sloughing, septic hernia protruding from the back of his head, to all appearances involving the whole of the occipital lobes. The parietal bones were loose and could be moved under the scalp. On the following day he was quite collected, though suffering from pain in the head and neck, and to rough testing he was totally blind.

On March 28 the patient said he saw something moving on his right, which proved to be his wife's shadow on the wall. When tested, he could distinguish between light and darkness, and could detect finger movements in the upper part of the periphery of the right superior quadrants. Stationary objects, form and colour were not perceived.

He was totally blind in the rest of his fields, and no attempt was made to chart the seeing parts as it was naturally impossible for him to fix. Later, when he began to get out for walks, he noticed that he could detect movements as he passed objects, e.g., lamp-posts, on his right side. He said: "They don't appear to have any colour or shape. They look like shadows. Sometimes I can tell if the moving things are white."

On November 4 his vision was exactly the same. He was aware of movement in the same limited part of the field; but he had no idea of shape, and he could not count fingers.

This case is of interest in so far as it shows that what remained of vision was for movement and light stimuli only, and this was confined to a small part of the upper peripheral field.

Group 2.—Showing Recovery of both Perceptions, though in Different Degree.

Four cases are included in this group. The first demonstrates the dissociation and partial recovery of vision for object and movement stimuli in complete homonymous hemianopia, the second in altitudinal hemianopia, the third in concentric contraction of the fields, and the fourth in quadrantic defect. The order of return of the two perceptions is well illustrated.

Case 6.—Lieut. C. received a bullet wound in the occipital region, on October 17, 1915. He recollects nothing of what happened during the next three days. He came to himself in No. 14 Stationary Hospital, Boulogne, and discovered that he was completely blind. On October 21, two days after his arrival at Boulogne, Lieut.-Col. Sargent operated.

Two days after operation the patient could distinguish between light and darkness. Sight in the right half fields gradually improved. Unfortunately he could not remember which perceptions came back first. He was still blind in the left half fields.

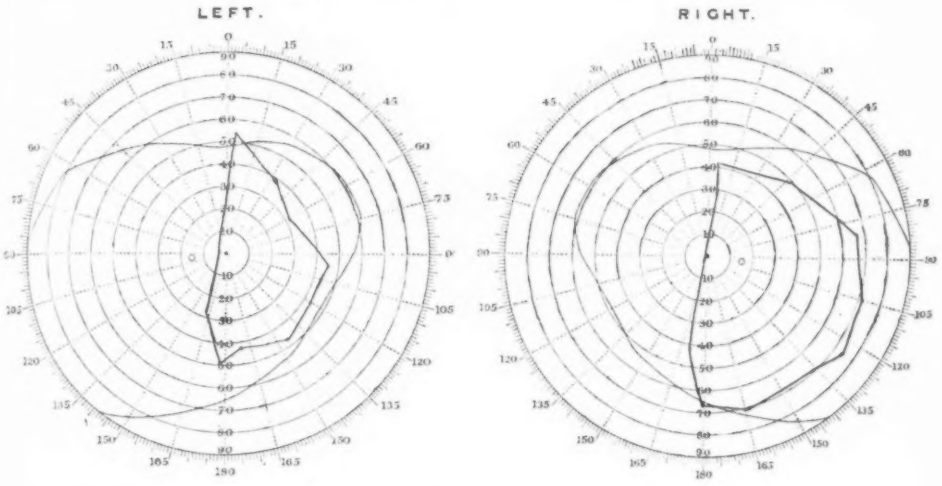
Transferred to England on the ill-fated "Anglia," he was in the water for ten minutes after she was struck. When admitted to the Empire Hospital, on November 17, 1915, under Dr. Guthrie, he was suffering considerably from shock.

Fig. 13 was taken three days after admission, when he was still in a very nervous condition. The fields, as are also those of the next chart, are for object perception only.

Fig. 14.—Twelve days after admission, and six weeks after injury. He is completely blind in the left half fields to the stimulus of a stationary object, except for a small strip in the left upper quadrant, more noticeable in the field for the left eye.

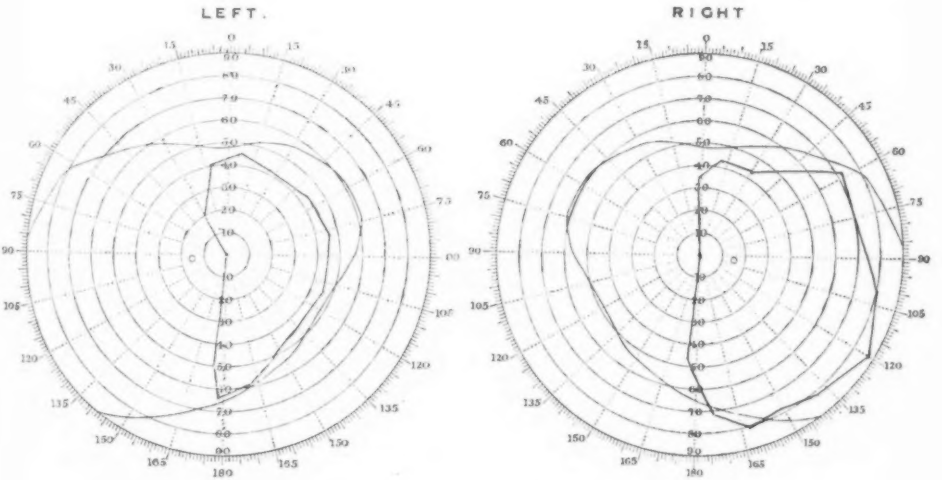
Fig. 15.—Three months after injury. The fields are for movement and object vision. The field for the perception of an object shows practically no change; but movement can be detected in quite half of the upper quadrant. The left eye field brings out a small blind area in the right lower quadrant immediately below the fixation point.

Fig. 16.—Four months after injury. Central vision $\frac{6}{6}$, right and left. The field is for movement perception only. There is now peripheral vision for movement in the lower quadrants, and a large paracentral scotoma remains, occupying part of both lower quadrants, chiefly the left. Movement is perceived in the whole of the left upper quadrant.



= Field for recognition of the object.

FIG. 13.



= Field for recognition of the object.

FIG. 14.

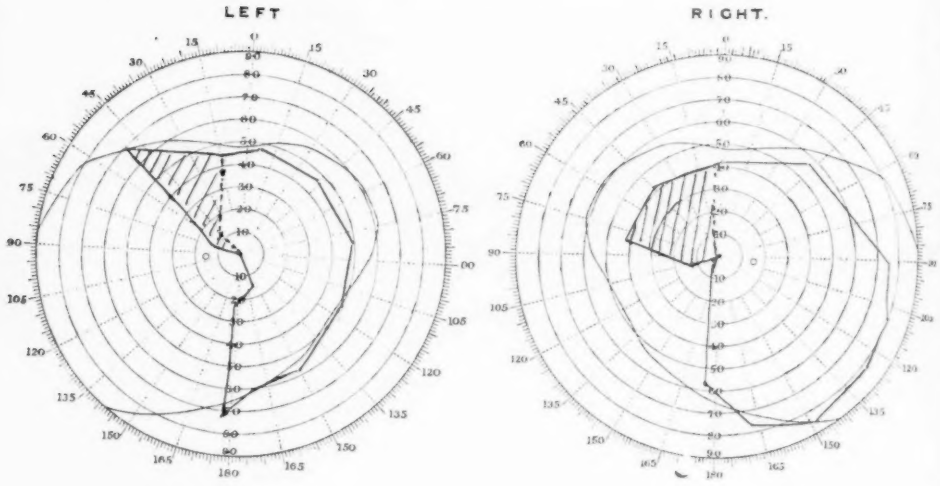
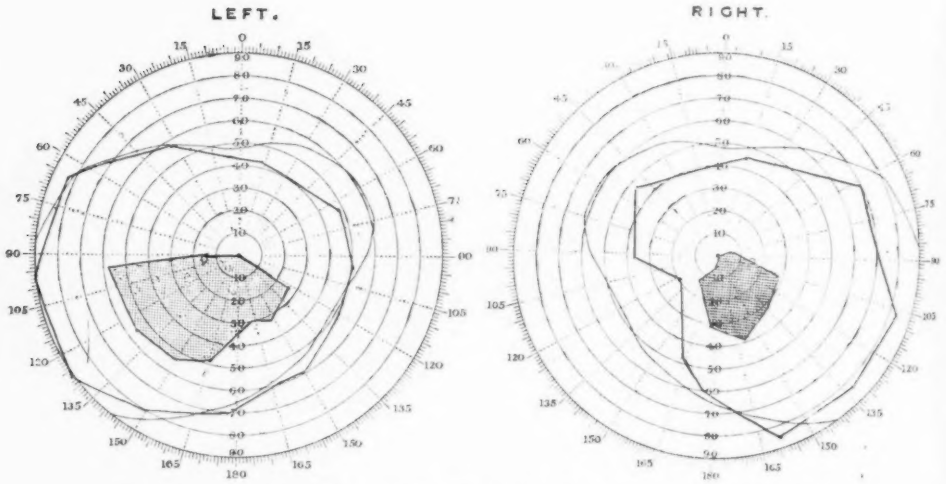


FIG. 15.



The field for appreciation of movement is represented with a large scotoma occupying the central part of the lower half field.

FIG. 16.

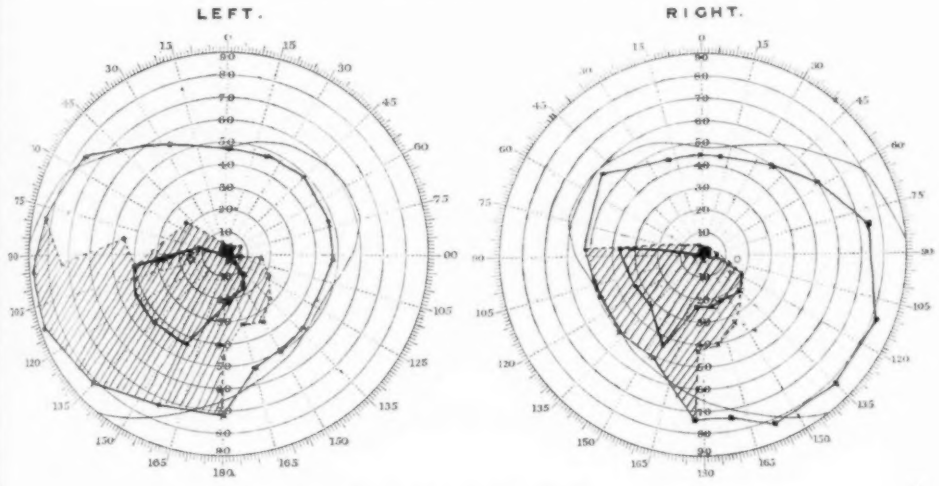

LEFT.
RIGHT.
= Object not recognized.
= Movement not recognized.

FIG. 17.

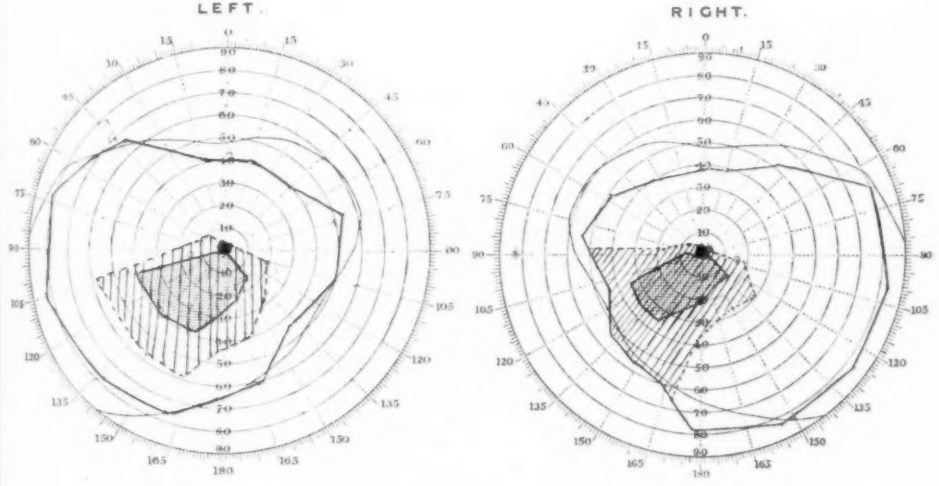
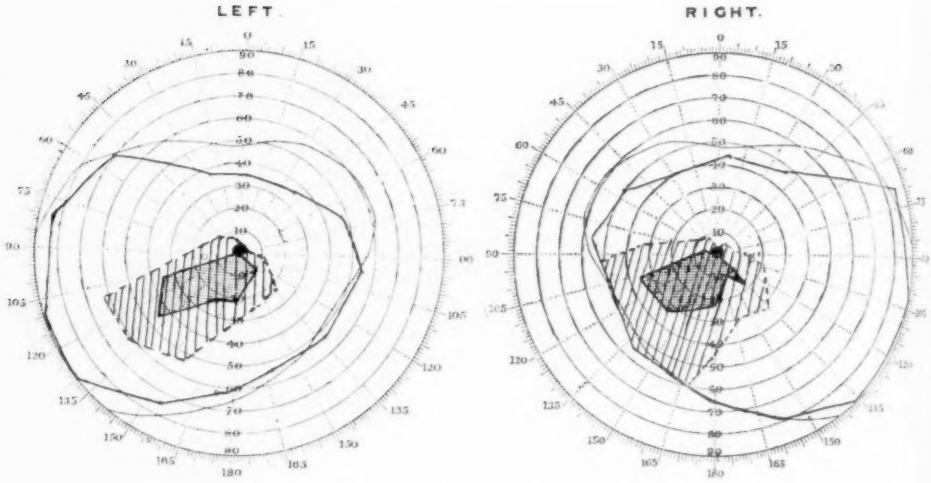

LEFT.
RIGHT.
= Object not recognized.
= Scotoma for movement.

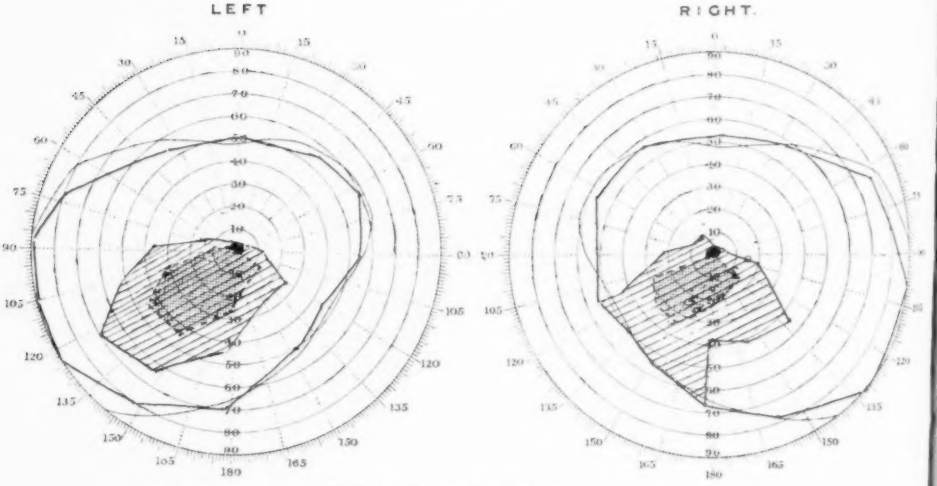
FIG. 18.



= Scotoma for object.

= Scotoma for movement.

FIG. 19.



= Scotoma for object.

= Scotoma for movement.

FIG. 20.

Fig. 17.—Five months after injury. The fields for both perceptions are represented. Object vision has extended into practically the whole of the left upper quadrant, but it is still lost in the left, and in part of the right lower quadrants. The scotoma for movement is pretty much as in Chart 4. It is observed that the perception of "a something moving" recovered before the object was recognized.

Careful repeated examination brought out that central vision was retained for all forms of stimuli, in both upper quadrants, and to some extent in the right lower quadrant, to a distance of about 3° from the fixation point.

Fig. 18.—Seven months after injury. The field for central vision has not expanded. Object vision is now present in the peripheral field of the left eye but not of the right, though it shows signs of creeping into the lower part of the quadrant from below. The defect in the right half field is noticed, as in the previous chart, to be greater for the recognition of an object than for appreciation of movement.

Fig. 19.—Eight months after injury. The object field for the right eye is extending along the margin from above and below. The scotoma for movement is less in both charts.

Fig. 20.—Ten months after injury. In the right eye chart the field for object vision has extended still further into the upper part of the left lower quadrant, but it has lost ground a little below.

Points to be noted in this case are:—

(1) That the recovery of vision for movement preceded that for the object.

(2) That the amount of recovery was greater for movement than for the object.

(3) That the remaining loss was a paracentral scotoma, vision having come back first in the peripheral parts of the field.

(4) That what remained of central vision was in the upper quadrants, the scotoma in the lower part of the field reaching the fixation point.

Case 7.—Capt. H. was wounded on September 15, 1916, by a piece of high explosive shell in the mid-occipital region. He was "black" blind for five days. Admitted to No. 2 Red Cross Hospital, Rouen, on September 20, he was operated on on the same day by Major Austin. September 21: He could distinguish between light and darkness, and saw "something moving" when the nurse was feeding him with a spoon. Stationary objects, form or colour, were not perceived. September 22: Could distinguish the nurse's face from her body. September 23: Could see, in a dim way, a lamp which hung from the ceiling, about 7 or 8 ft. in front of him. September 27: He was able to decipher a notice, in large print, on the wall facing him, about 12 ft. away. He could see but one word at a time.

Vision gradually returned in the upper quadrants, the recognition of "some-

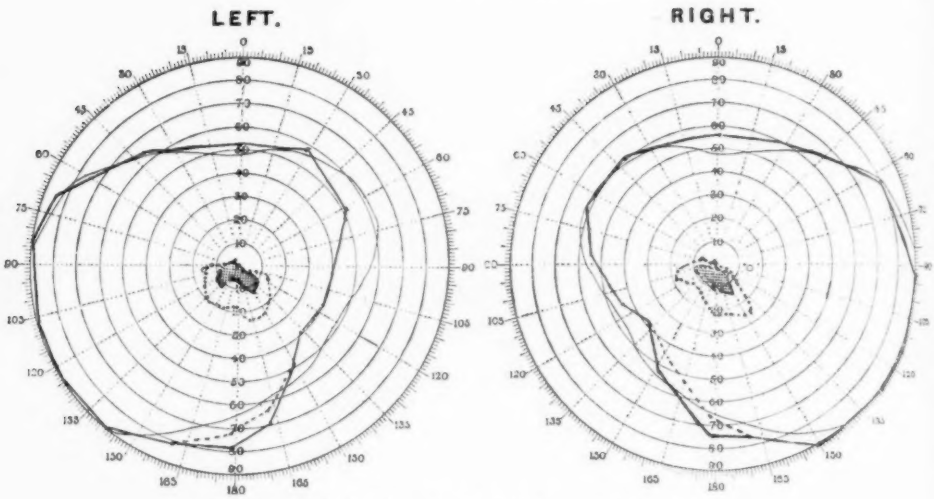
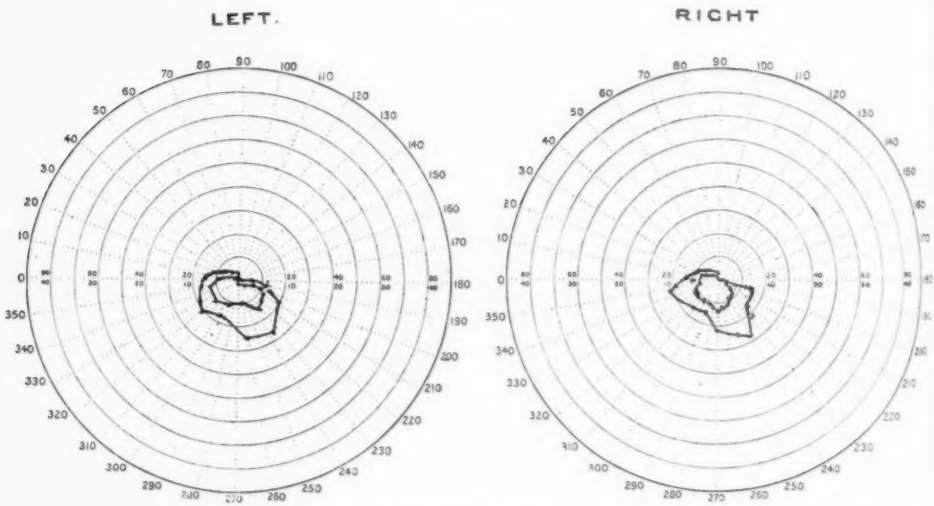

LEFT.
RIGHT.
= Central scotoma in the field for recognition of object.
= Central scotoma in the field for appreciation of movement.

FIG. 21.



At 1 metre. The scotomata are represented, the smaller for appreciation of movement, and the larger for recognition of the object.

FIG. 22.

thing moving" coming first with the ability to distinguish between light and darkness. A stationary object was next perceived as a faint blur, then its form, and last of all its colour. He volunteered the information that the amount of vision varied from time to time, being more at one time, and less perhaps a few minutes later. It was not to be depended on.

He was transferred to Queen Alexandra Military Hospital, Millbank, and on November 20 he noticed he could see "movements" near the ground when people were passing him. In a few days he was able to recognize the "moving things" as feet.

Capt. Heron kindly sent him to me on November 29 for examination, and I charted his fields the next day, with the McHardy perimeter.

Fig. 21.—Central vision $\frac{6}{12}$ right, partly, and $\frac{6}{9}$ left. The charts show two central scotomata, which occupy both lower quadrants, and reach the fixation point. The scotoma in the field for the recognition of the 1 cm. white square extends to about 20° from the fixation point, while that for movement goes only just beyond the 10° circle.

Fig. 22.—The records were corroborated by the Bjerrum screen. The scotomata mapped out by the two different methods are almost exactly the same.

These records show that even where the visual loss is limited to a small portion of the field the dissociation can be demonstrated.

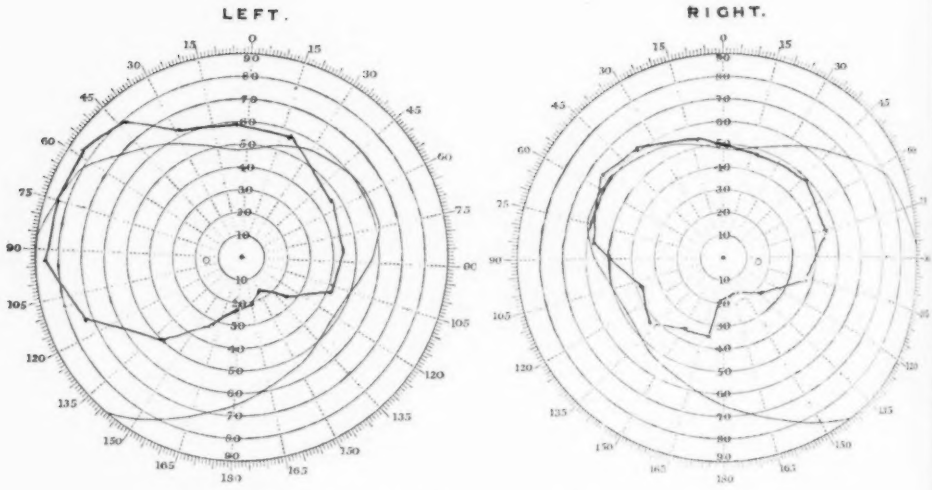
Case 8.—Lieutenant H. was wounded by a bullet in the occipital region on July 13, 1915. He was unconscious for three days, and during that time he had been operated on at Merville. From the scanty information on the transfer sheet, I gathered that the entry wound had been enlarged, and the bullet, which was lying well forward between the occipital lobes, was removed, along with a few small pieces of bone, some of which had followed the bullet, and some had remained superficial.

The patient, who had sensory and motor loss in both legs below the knee, noticed nothing wrong with his vision for about a month; but during that time he had been kept in bed. His difficulty was in seeing things to the right and on the ground. When he walked, he stumbled over objects as high as his knee, unless he kept his eyes fixed on the floor. He had the same difficulty in avoiding things situated on his right side.

He was admitted to the Empire Hospital under the care of Dr. Kinnier Wilson, and on October 5 a record of his fields for the recognition of movement was made.

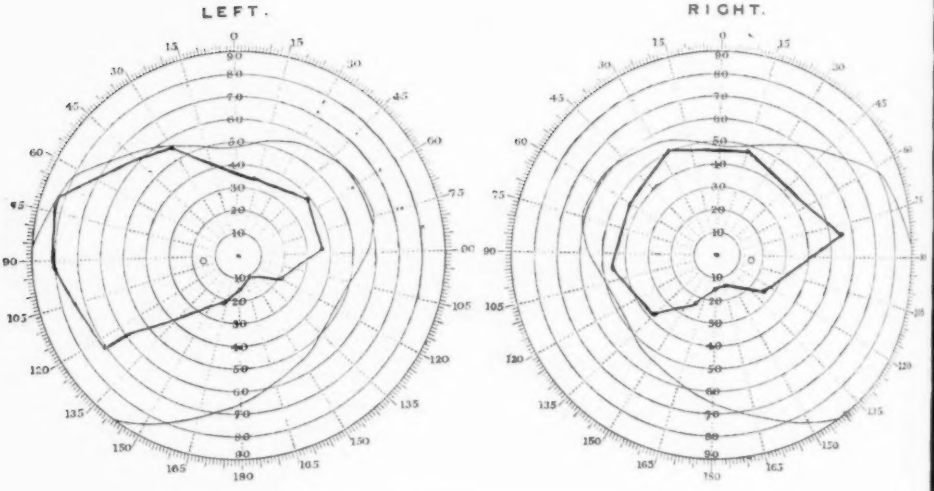
Fig. 23.—Central vision $\frac{6}{9}$, right and left, two months after the injury. The defect was shown to be mostly in the lower quadrants, though the right upper quadrant was also restricted.

He was discharged on October 30, and while on leave his wound reopened. He was again admitted to the Empire Hospital on January 21, 1916, complaining of nausea in the morning, and occasional frontal headaches and dizziness. He did not think his eyesight had got more restricted, but he noticed the defect more.



= Field for appreciation of movement.

FIG. 23.



= Field for appreciation of movement.

FIG. 24.

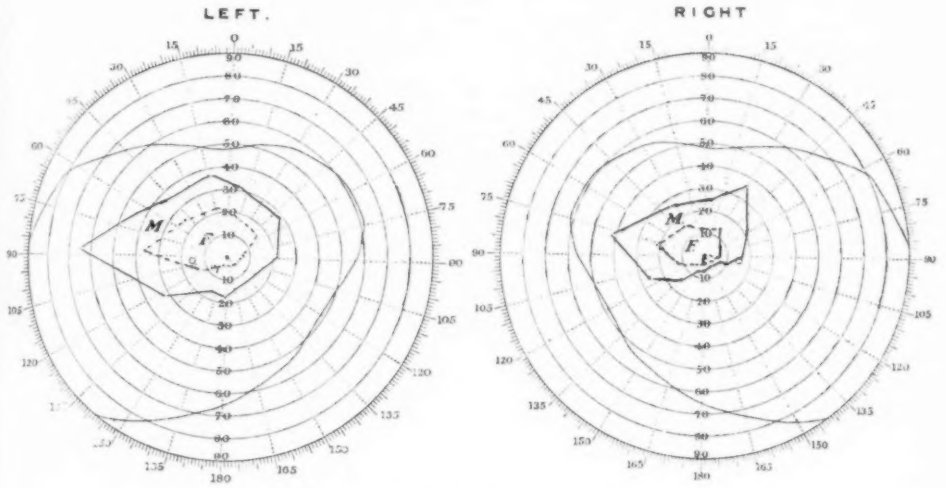
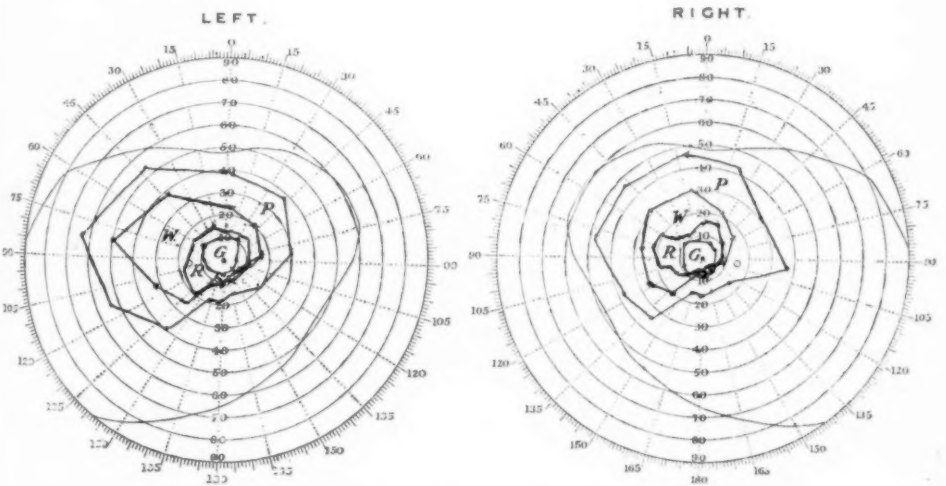


FIG. 25.



The line surrounding "P" limits the field for appreciation of movement. The field for recognition of the object is enclosed by the line which surrounds "W."

FIG. 26.

Fig. 24.—The fields for movement were charted four days after his admission, and the loss was found to be if anything a little greater, especially in the lower quadrants.

Fig. 25.—On February 9, a record was again made of the fields. They showed a marked general restriction, most pronounced in the lower quadrants, and more especially in the right. The fields for stationary objects and for movement were completely dissociated, the movement field being the larger. The patient had practically telescopic vision.

Two small fragments of bone were localized, by X-ray examination, in the great longitudinal fissure, and on February 3 Mr. Walton removed them.

Fig. 26.—Six days later the fields for the recognition of movement and object were found to have enlarged considerably, and the increase was relatively about the same for both.

When he was discharged on April 26, the fields were *in statu quo*, but as he had got accustomed to moving his eyes about more freely, his visual defect disturbed him much less.

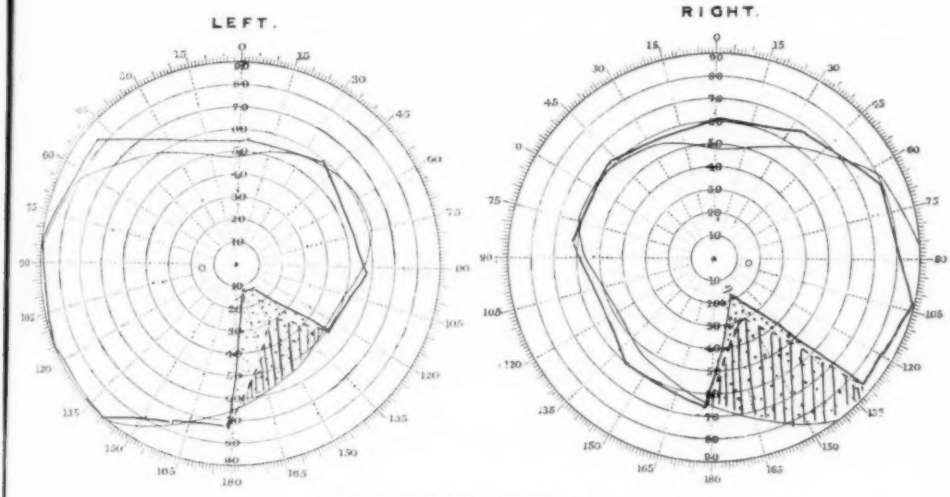
Case 9.—Captain R. was wounded on July 25, 1916, in the occipital region, by pieces of shrapnal casing. He was walking at the time the shell pitched behind him. His limbs were not affected, but he noticed at once that he was blind in both lower quadrants. He walked back to battalion headquarters, a distance of three miles, and to avoid stumbling over obstacles he had to keep his eyes fixed on the ground. After having his wound dressed, he walked three miles to the field ambulance, experiencing the same difficulty with his vision.

At No. 2 Red Cross Hospital, Rouen, Major Austin removed two pieces of metal, and raised a depressed fracture on July 28. A week after the operation, the patient noticed some return of vision in the left lower quadrant. He is quite certain that recovery began in the peripheral field, and that he recognized light and movement only. He could not see stationary objects. The improvement in the left lower quadrant went on till the whole quadrant recovered. Movement, he says, was perceived before stationary objects, form or colour.

He was admitted to the Empire Hospital on August 6, under Dr. Buzzard. On roughly testing the visual fields with my fingers, I found that part of the right lower quadrant was defective. The loss, which appeared to be more for a stationary object than for movement, did not reach the fixation point.

Fig. 27.—Central vision $\frac{6}{6}$, right and left. One month after the date of the injury. The apex of the wedge in the inferior part of the quadrant reaches to between 10° and 20° of the fixation point. The fields for a stationary object and for movement are dissociated, the former having suffered more than the latter. The left lower quadrant has recovered completely.

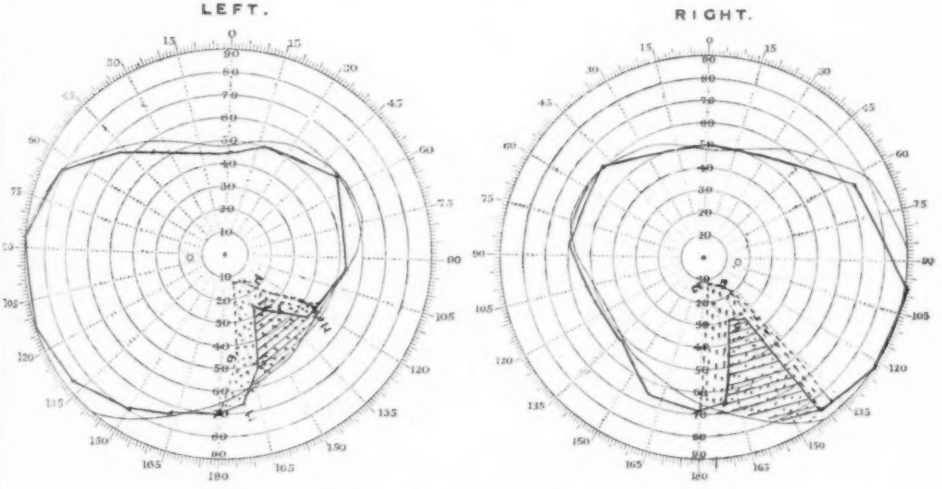
Fig. 28.—Three and a half months after the injury. A little improvement is demonstrated in the fields for both perceptions, more noticeable in the field for movement; the filling out of the fields is more at the periphery, so that the base of the wedge is narrower. Colours are not appreciated in the affected part of the field.



= Object not recognized.

= Movement not recognized.

FIG. 27.



= Object not recognized.

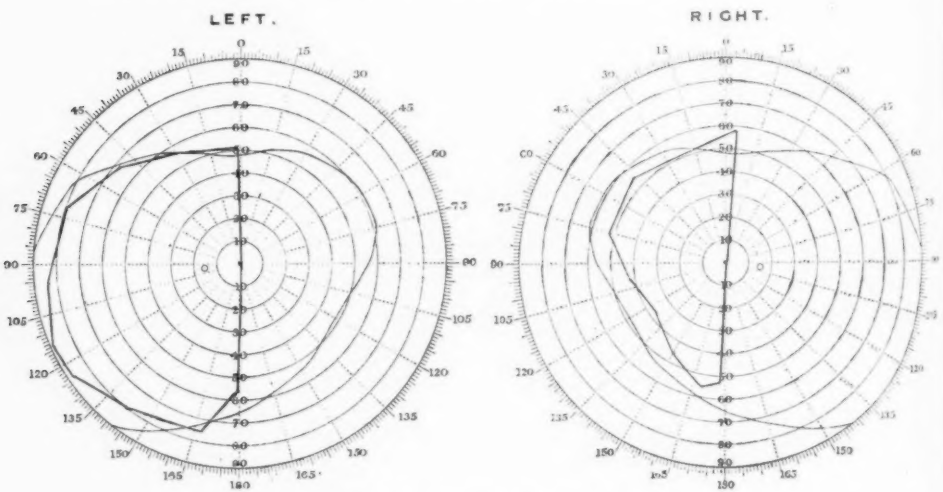
= Movement not recognized.

FIG. 28.

Group 3.—Where no Dissociation or Recovery of Vision occurs.

Certain cases of hemianopia, however, show no dissociation of object and movement vision, and remain stationary, at all events for many months. But I have found them to be relatively few in number, and only one occurs in this series of cases. One might suggest, tentatively, that coincidence of the two fields and the absence of any sign of recovery are due to the injury being more extensively subcortical. I cannot bring forward pathological material to prove this assertion, but Swanzy [7], writing on relative hemianopia, said that he believed it was the result of a lesion of less intensity than that which caused absolute hemianopia. The following case belongs to this group:—

Case 10.—Lieutenant M. was wounded at Loos about September 30, 1915, by a rifle bullet in the left occipital region. On admission to the Rawal Pindi Hospital, the next day, he was in a semi-conscious condition, quite unable to give the name of his unit or his people's address. Later, during a fairly lucid period, he demonstrated to the doctor his right hemianopia.

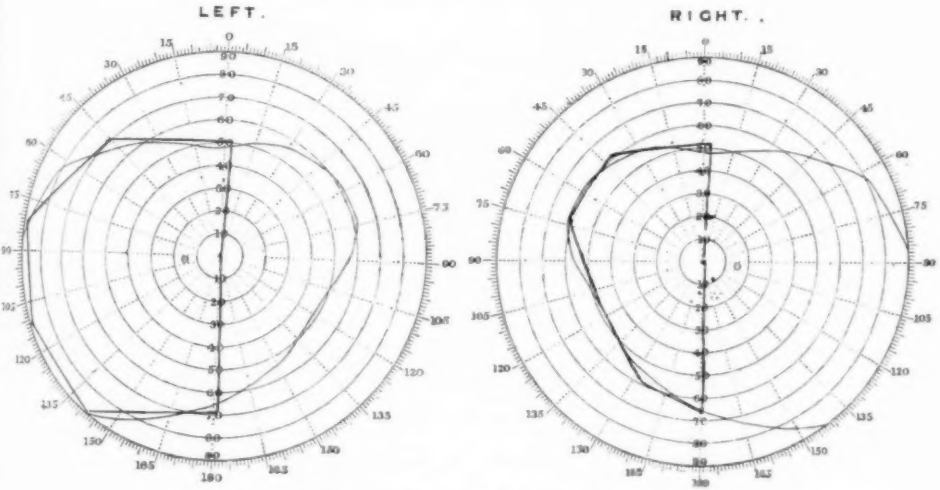


The fields for appreciation of movement and recognition of the object are coterminous.

FIG. 29.

On November 2 he was admitted to the Empire Hospital, under the care of Dr. Collier. The fields, charted on November 13, showed a right homonymous hemianopia, up to the fixation point. The object and movement fields entirely coincided.

Fig. 29.—Central vision $\frac{3}{6}$, right and left. Records of the visual fields were taken at intervals till June, 1916, and no change could be detected The last only need be shown (fig. 30).



The fields for appreciation of movement and recognition of the object are identical eight months after the patient was injured.

Fig. 30.

The points I have tried to demonstrate in this chapter may be summarized as follows:—

(1) In restricted visual fields from occipital injuries where some recovery of vision occurs, the first visual stimulus perceived, which can be recorded on a chart as a field is movement.

(2) Recovery of vision for movement begins in the peripheral field.

(3) Appreciation of movement and recognition of an object are always dissociated in patients in whom recovery of vision can be demonstrated; the field for the former, which is the more primitive perception, being the larger.

(4) In prognosis this dissociation is a valuable aid, for when it is absent after a few months have elapsed no recovery of vision occurs.

(5) The relative sizes of fields are the same whether the test object be black or white, used against a black screen, and whether it be 1 cm. or 15 cm. in diameter.

Light and movement are probably the most primitive of all visual percepts, and consequently one would have expected that they would be

perceived first in a recovering blind field. Recognition of movement is essential to animals both for hunting and for self-preservation; thus naturally it would have a wide field, and its recovery would begin in the periphery of the field. The peripheral and wider fields receive stimuli which inform the individual that there is "a something" within his visual range; if he considers that this "something" should be investigated further as to its distance, its colour, its shape, its size, and its dimensions, then he brings central vision to bear upon it. Any one who has shot at driven birds can illustrate this from his own experience. While getting a bird with the right barrel, you are suddenly conscious of something moving far out on your left. Though you recognize only movement in "the something," you immediately connect it with another bird, and swing round to corroborate your surmise and to get it with the other barrel.

The dissociations between the perceptions of these primitive and elementary visual sensations are, I venture to think, comparable with those which are found from interruptions of somatic sensory paths; though I fully recognize the essential difference between the mechanisms of production of visual perceptions and skin sensations, in that the receptors of stimuli which originate the one react to objects at a distance; while the receptors of stimuli which originate the other react to objects in contact with the skin. The visual sense, like the senses of smell and hearing, has become highly specialized for the performance of particular functions, through the special development of the receptors of the leading segments for reaction to distant stimuli, as pointed out by Sherrington [5]; yet, clinically, the types of dissociations can be compared with those of ordinary sensation in so far as they result from disturbance at the higher physiological levels of the respective afferent sensory systems.

As I shall endeavour to show in the next chapter, a further analogy can be drawn between the dissociations of the higher and more evolved functions of vision and those of sensation which result from cerebral injuries.

Chapter III.—Visual Orientation and Stereoscopic Recognition.

Smith and Holmes [6] have given a very full description of "a case of bilateral motor apraxia with disturbance of visual orientation." The patient was a soldier who received a shrapnel bullet wound of the head, the entry being in the right post-central vertex and the exit in the left temporal region.

Amblyopic in part of both lower quadrants for the recognition of a white object 10 mm. square, he could frequently appreciate movements in the defective area of the field; so that perception of movement and recognition of object were dissociated. He was unable to orientate in space the positions of objects seen in the extra-central parts of the retina, and the relative positions of objects that came in succession into central vision. Also, objects outside central vision failed to excite his attention.

Case 3 of this series presents many symptoms which are parallel to those described by Smith and Holmes. He was, as already mentioned, blind in the left half fields, though now he can appreciate movements in the periphery of their lower quadrants. His ability to orientate in space things that he sees quite well is almost entirely lost, and thickness and depth mean nothing to him visually. He has lost stereoscopic vision.

I will describe his symptoms in detail as they seem to throw light on the nature of stereoscopic vision and on the relation of cerebral defects of vision to those of general sensation.

In the earlier months of his illness, he was quite unable to combine simple movements into complete purposive acts with his right hand and arm. He had, it is true, some weakness and sensory loss of the right side, and for this reason I suppose his symptoms should not be described as apraxic; but the disability was out of all proportion to the amount of paresis and loss of sense of position. From the first there was no agnosia. He still hesitates before he uses things correctly with his right hand. Purposive movements lack spontaneity. The disability has always been, so far as can be ascertained, limited to the right side.

Though he has no difficulty in bringing objects which he sees at once into central vision, this was not always so; for when in hospital at Alexandria he was frequently unable to get his eyes fixed on anything he was asked to look at, even when he knew quite well its position in space, e.g., his hand.

He quickly looks in any direction to order or when a light is suddenly flashed from either side, or a sudden noise made. Strictly speaking, however, he does not rotate the eyes, but turns his head, keeping his eyes more or less stationary. Similarly when asked to follow a finger with his eyes, though he has no difficulty in keeping them fixed on it, the movement is not of the eyes but of the head. He said in explanation: "I am so accustomed to moving my head about

when I read that I do it unconsciously." He has no trouble in keeping his eyes fixed on an object when his head is passively moved; nor in following it with his eyes when his head is kept fixed by the observer.

On being asked to explore the surface of a table with his eyes and to count the coins placed on it, he did it correctly. He believed however, that this would have been impossible for him in the earlier days of his illness.

His visual memory is apparently intact; and, at all events now, his ability to retain visual impressions is not affected, e.g., when a box, a pen, a test-tube and a patellar hammer were shown to him in quick succession and then hidden he described them accurately. There is no visual agnosia.

Visual orientation, however, is grossly upset. He is unable to localize in space the position of an object seen. When told to take hold of a matchbox which was held in front of him, though he saw it at once and kept looking at it, his hand groped about searching for it before it was finally grasped. The task was equally difficult whichever hand he used. He makes poor attempts at touching a spot on a piece of paper with his finger, and the plane in which the paper is held makes no difference.

The length of a room, in reality 18 ft., was thought by him to be 30 ft. Sitting about 3 ft. away from him, he said we were separated by a distance of at least 6 ft.; but he declared he was only guessing as he had no real idea of my relation in space to himself. He can tell only if an object is very near or very far away. He is able, however, to judge with a fair degree of accuracy the height or length of different objects, e.g., a walking-stick, a pencil, a house, but occasionally he makes gross mistakes.

Similarly, he is unable to estimate correctly relative distances and lengths. On a piece of paper held flat on a table before him, two large dots 4 in. apart and one nearer to him than the other, appeared to him to be side by side. When the dots were placed equidistant from the eyes, by shifting the paper round they were recognized to be so. The relative position of the two dots was, nevertheless, easily recognized when he was allowed to move his finger from the one to the other. His answers are equally wrong whether the objects are far away from him or near to him. He never says that the nearer object is the more distant.

Curiously enough, however, he can choose correctly, often several times in succession, the longer of two lines drawn on paper, irrespective

of whether they are parallel or not. But if tested with the same lines a short time afterwards he may give a series of answers which are mostly incorrect. It is impossible to predict what his answers will be. With the line tests he appears to have, if anything, more difficulty when the paper is held some distance from him, say 6 ft. away, than when it is nearer.

When I was carrying out some of the tests one day he suddenly said: "Everything seems to be really the same distance away. For example, you appear to be as near to me as my hand" (he was holding his hand $1\frac{1}{2}$ in. from his face and I was sitting about 5 ft. away from him). This loss of appreciation of the relative positions of things that he sees quite well has been the means of giving him many a fright. Two vehicles approaching one another in the street always seem to be about to collide. A person who is crossing the street is sure, he thinks, to be run over by a taxi that is really yards away. He used to stand and stare aghast till he found he was registering wrong impressions, and that the accidents which he expected to occur every minute did not come off. If two people walking together come towards him on the pavement and separate to let him pass, he loses sight of the one who goes to his left, as he is almost completely blind in the left half field, and very frequently walks into the one on his right. He can see the man but he cannot judge how far away he is. When waiting with his wife to cross the street, the houses on the other side, the policeman and the refuge all seem to be the same distance away and quite near to him.

His most interesting defect is inability to appreciate depth or thickness in objects seen. The case described by Smith and Holmes had not apparently this difficulty, for they make no mention of it; so that visual localization and orientation may be dissociated from visual appreciation of depth. This symptom, in Captain de W., is very pronounced, and is a source of great trouble to him. The most corpulent individual might be a moving cardboard figure, for his body is represented by an outline only. He has colour and light and shade, but still to the patient he has no protruding features; everything is perfectly flat. One of the unfortunate results of this phenomenon is that friends are recognized only by their voices. A man can be distinguished from a woman because, on account of his dress, his outline is different, and he may possibly wear a beard or a moustache.

To the patient a chair is flat, though he knows from experience that his visual impressions are cheating him. Similarly a sphere is merely a circle, a cylinder a flat rectangle, a cube a square, and a pyramid a triangle. He appreciates shape perfectly.

A stair is a flat inclined plane with no protruding steps, and yet he knows from the light and shade that he ought to see the steps. It was only a few months ago that he began to recognize visually that the top of the flight was farther away from him than the bottom, when he stood a few feet away and looked at it. A landscape is like a painted picture or a piece of stage scenery. I was walking along the street with him on a bright day, when the pavement threw a deep shadow, and he mentioned that strictly speaking the pavement did not seem to him to be elevated above the street. He quite realized that the shadow meant that it was so, but, as he put it, "something else that indicates depth has been taken away, and, despite the difference in light and shade, to me they are both on the same plane."

Hollow vessels appear to have simply shape and no depth. Looking into a kidney-tray he sees only a flat kidney-shaped white metal plate, part of it in the shade and part not. Similarly a bowl viewed from the side is a flat semicircular disc, and if presented to him face on is a circular plate.

His visual pictures are just the same whether he examines objects with one or with both eyes; but immedietely he uses his fingers he can tell that the things have depth as well as shape.

The visual defects shown by this case and by several others in the literature seem to me to be analogous to the defects in spatial discrimination found in sensory disturbances of cerebral origin.

Summarizing briefly the defects in visual orientation and in visual appreciation of depth which this patient shows, they are:—

(1) Inability to localize an object which he sees; he can only distinguish whether it is very near or very far away.

(2) Inability to tell which of two objects is the nearer to him; provided they are not separated by a great distance, they appear to be equidistant from him. He never chooses the one which is the farther away as being the nearer of the two. On the other hand, he frequently chooses correctly the longer of two lines drawn on a piece of paper, or the taller of two persons who are standing near one another; but he shows a certain inconstancy in this, so that one cannot foretell whether an answer will be right or wrong.

(3) Inability to appreciate visually depth and thickness in objects, notwithstanding perfect consciousness of light and shade and possession of binocular vision. In his own words, "Something else that indicates depth has been taken away."

He can, however, describe correctly the forms of different objects

which are presented in his visual field, e.g., a rectangle, a circle, a square, or a triangle.

Defects in spatial discrimination, similar in type to the visual dissociations enumerated above, are evident in his right hand.

(1) Localization of a touch is defective in the first three fingers.

(2) Each finger has to be passively moved on an average through eight or nine degrees before he is conscious that the position has been altered; whereas he recognizes a change of posture when a finger of the left hand has been moved through one degree.

(3) Appreciation of relative thickness of things is not nearly so acute with his right as with his left hand, e.g., when he was given, one after the other, two spheres of unequal size to feel with his right hand—though their diameters differed by almost $\frac{1}{2}$ cm., he thought they were the same. He chose the larger of the spheres quite readily when he was tested in the same way with his left hand.

Discrimination of weights and estimation of shape are not measurably impaired; neither is the appreciation of two compass points when they are separated by 1 cm. and applied simultaneously.

It would appear from this and similar cases which have been recorded that stereoscopic vision depends on something more than the possession of binocular vision and the ability to appreciate differences in light and shade.

Chapter IV.—Situation of the Lesions.

Rifle, machine-gun and shrapnel bullets, pieces of high explosive and bomb-shell casings, together with indriven bone fragments and depressed fractures, have been the destructive agents. The wounds were of the penetrating, perforating and gutter varieties. Operations had been performed in most cases either at the casualty clearing stations or at the base hospitals; but as a rule some indication was given on the transfer sheet or on the medical history paper of what had been done, and also of the extent of the visual defect in the earlier stages of the illness.

I am fully aware that with head wounds it is almost impossible, without pathological material, to limit with accuracy the damage done to the brain, and particularly with injuries to the occiput, especially of the polar region. At the best only approximations can be made. Apart from the attempt to estimate how much brain substance has been destroyed by missiles and indriven fragments of bone, the presence or

absence of sepsis has to be taken into account. Moreover, vascular lesions are never absent.

In this paper I limit the use of the term, "injury to the occipital cortex," to cases in which the lesions are caused by localized depressed fractures, say, from gutter wounds, or by a piece of metal which has just perforated the skull but not the dura, and in which X-ray examination has excluded indriven fragments. Two cases in this series belong to this group; in the other eight the subjacent structures with the cortex have been involved.

In this chapter, a short description of the wounds, of the results of X-ray examination, and of the appearance of the brain at operation, will be given, together with the probable parts of the brain damaged.

Case 1.—*Entry.* A small perforation situated $\frac{3}{4}$ in. above the inion, and $\frac{1}{2}$ in. to the right.

Exit.—Represented by a trephine opening 2 in. in diameter with its centre $3\frac{1}{2}$ in. above and $\frac{1}{2}$ in. behind the opening of the external auditory meatus.

Nature of projectile.—Rifle bullet.

Condition of wounds.—Practically clean.

X-ray examination.—No loose fragments of bone seen.

A description of the operation was not sent with the patient.

On this evidence, the left occipital lobe was unaffected. The bullet entered the right lobe just on the occipital pole, which, according to Holmes and Lister, lies about 1 in. above the inion, and must have traversed the optic radiations obliquely. The lesion of the tip of the lobe corresponds to the involvement of the left half of the central field (p. 18).

Case 2.—*Entry.* Represented by a trephine opening 4 cm. long, and $3\frac{1}{2}$ cm. broad. Its centre is $4\frac{1}{2}$ in. anterior to, and $\frac{1}{2}$ in. to the right of the inion.

No exit wound.

Nature of projectile.—A piece of bomb casing.

Condition of wound.—Very septic.

Stereoscopic X-ray examination.—A shell fragment was localized $1\frac{1}{2}$ in. above and in front of the internal occipital protuberance, and 1 cm. to the right of the mid-line. No bone splinters were shown.

Operation.—At Rouen, on February 24, under local anæsthesia, the wound was excised and a small extradural collection of blood was removed. A hole in the dura was discovered, and was enlarged slightly. The tract was explored and the metal felt; but on an attempt being made to remove it the patient had a very severe general convulsion, and almost died on the table. The operation was abandoned.

The damage was probably confined to the left lobe. The lesion was well above the occipital pole, and central vision was retained (figs. 2, 3 and 4).

Case 3.—*Entry.* Represented by a trephine opening 1 in. diameter with its centre $5\frac{1}{2}$ in. behind the nasion measured along the nasio-inional line, and $1\frac{1}{4}$ in. to the left of that line.

Exit.—Trephine opening $1\frac{1}{4}$ in. in diameter. Its centre is $1\frac{1}{2}$ in. in front, and $\frac{3}{4}$ in. to the right of the inion.

Nature of projectile.—Shrapnel bullet.

Condition of wounds.—Both had been septic.

X-ray examination.—Some loose fragments of bone were lying superficially in the brain under the entry wound, and the bullet in the tip of the right occipital lobe.

Operation.—On January 7, 1916, the skull was trephined over the right occipital pole. The bullet was removed, and an abscess evacuated.

It is possible that the bullet in its course missed the optic radiations of the left lobe, but it must have passed through those of the right lobe. The formation of an abscess round the bullet points, however, to the greatest destruction of brain tissue having been in the polar region of the lobe. The clinical picture, it will be remembered, was an original left homonymous hemianopia up to the fixation point, with subsequent return of appreciation of movement in the periphery of the lower quadrant (figs. 5 and 6).

The position of the entry wound is interesting in view of the defects in visual and sensory orientation.

Case 4.—*Entry.* Trephine opening, measuring $1\frac{1}{2}$ in. horizontally, and just over an inch vertically, has its centre $2\frac{1}{2}$ in. above and $1\frac{1}{2}$ in. behind the opening of the left external auditory meatus.

No exit.

Nature of projectile.—Shrapnel bullet.

Condition of the wound.—Slightly septic, but healed quickly.

X-ray examination.—The bullet was localized $\frac{1}{2}$ in. above, $\frac{1}{2}$ in. anterior, and $\frac{1}{2}$ in. to the left of the inion. No splinters of bone to be seen.

Operation.—The entry wound was enlarged on board the hospital-ship which conveyed the patient to Malta, but the medical history sheet sent with the patient gave no information about the operation.

The bullet in this case had traversed the outer part of the left lobe, and came to rest just below and in front of the pole. The charts of the fields demonstrated a right upper quadrantic hemianopia, and some peripheral restriction of the lower quadrant. Appreciation of move-

ment returned except in a small area of the central field of the upper quadrant. There was no recovery, however, for the recognition of an object, or of form or colour (figs. 7 to 12).

Case 5.—The damage done to both occipital lobes was extensive. Many large and small pieces of bone were shown by the radiogram to be lying in the brain, some superficial, and some deep. There was much sloughing of brain substance, and the wound was very septic.

He was totally blind except for recognition of movement in part of the peripheral field of the right superior quadrant.

Case 6.—*Entry.* Represented by a large horizontally placed hernia, 3 in. long and $1\frac{1}{4}$ in. deep, lying across the mid-occipital line. Its centre was $2\frac{1}{2}$ in. from the inion.

No exit.—The wound was probably of the in-and-out variety, with a large depressed fracture.

Nature of projectile.—Rifle bullet.

X-ray examination.—In the plates, taken after his admission to the Empire Hospital, no loose splinters of bone could be seen.

Operation.—I am indebted to Lieutenant-Colonel Sargent for the following note: "A large occipital flap was turned down and many small fragments of bone were removed, partly from the under surface of the flap and partly from the left occipital lobe. The missile had divided the longitudinal sinus, the thrombosed stumps of which could be identified. On the left side the lesion lay $1\frac{1}{2}$ in. above the inferior border of the occipital pole and close to the mid-line; a cavity filled with debris of brain and fragments of bone passed inwards to a depth of an inch, its whole size being sufficient to admit the last joint of the forefinger.

"On the right side, the lesion was at the same level, but clearly more superficial and with no indrawn fragments of bone.

"After excision of the scalp wounds, the resulting gap was partly closed by a pericranial floor, leaving room for the passage of a metal drainage tube into the cavity in the left lobe."

The clinical picture does not correspond to the apparent relative damage of the occipital lobes as found at operation. It is to be noted, however, that the longitudinal sinus was badly injured and possibly there was an extensive thrombosis of the right occipital vein (figs. 13 to 20).

The parts of the visual areas above the calcarine fissures and immediately in front of the poles probably suffered most damage.

Case 7.—*Entry.* A round hole $\frac{3}{4}$ in. in diameter, over the right occipital lobe. The centre of the wound was $1\frac{1}{2}$ in. above and 1 in. to the right of the inion.

The piece of metal was sticking through the bone.

Nature of projectile.—Piece of high explosive shell casing.

Condition of wound.—Not very septic.

X-ray examination.—Large pieces of metal lying half in and half out of the skull, which is fractured for about 1 in. above and ½ in. below the hole. The metal protrudes into the skull for about 1 cm. No indriven fragments.

Operation.—Major Austin's note says: "Wound excised, shell and bone removed: very smart hæmorrhage. Dura not injured except for a small perforation of the lateral sinus. The shell had entered the right side and passed across to the left, but more bone was injured on the right side. Well cleaned. Lateral sinus sealed up with a flap of fascia lata, which adhered satisfactorily in ten minutes."

One might assume that little more than the cortex of the visual areas above the occipital poles was seriously injured. In two and a half months vision has returned in the whole fields, except in the lower quadrants of the central fields, to between 20° and 30° of the fixation point. The scotoma is larger for the recognition of an object than for appreciation of movement (figs. 21 and 22).

Case 8.—Entry. In the nasio-inional line 4 in. from the external occipital protuberance, and ½ in. to the left. The trephine opening round the wound is about 1 in. in diameter.

A sinus leading from the wound passed downwards and a little forwards for about 1½ in.

Nature of projectile.—Rifle bullet.

Condition of the wound.—Septic. The sinus exuded a little thick pus.

Stereoscopic X-ray examination.—Two small fragments of bone were localized in the great longitudinal fissure, about ½ in. behind the splenium of the corpus callosum and 1½ in. from the trephine opening.

Operations.—(1) At Merville not more than three days after he was wounded. From the scanty information on the transfer sheet, I gathered that the entry wound had been enlarged, and the bullet, which was lying well forward between the occipital lobes, was removed together with a few small pieces of bone. Some of these had followed the bullet and some had remained superficial.

(2) On February 3, Mr. Walton operated. A flap, cut round the original wound, was thrown down and the opening in the skull enlarged. A probe was passed down between the hemispheres, and two small pieces of bone were felt lying close together in the position localized by

the radiograms. They were easily removed, the larger being a little over $\frac{1}{4}$ in. in length and $\frac{1}{8}$ in. broad.

Holmes and Lister [4] have suggested "that the peripheral zones of the retina from its centre outwards are represented in serial order from behind forwards in the visual area," and I venture to think that this case brings forward further evidence in support of this view. Since the bullet and the splinters of bone lay in the fissure between the occipital lobes, it is probable that the damage was confined to the cortex and the innermost fibres of the optic radiations. Further, when the positions of the wound and the bullet and splinters of bone are considered together with the depth and direction of the sinus, it is likely that the posterior parts of the visual areas were uninjured. One may then assume from the clinical evidence that the peripheral contraction of the fields resulted from damage to the anterior parts of the areæ striatæ (figs. 23 to 26).

Case 9.—Gutter wound with a localized depressed fracture below. A trephine opening, measuring $1\frac{3}{4}$ in. horizontally and 1 in. vertically, has its centre just to the left of the mid-line and $3\frac{1}{2}$ in. above the inion.

Nature of projectile.—Pieces of shell casing.

Condition of wound.—Slightly septic but the dura was not perforated.

X-ray examination.—No indriven fragments of bone.

Operation.—Major Austin, on July 28, removed two foreign bodies which were lying against the skull. As he found a localized depressed fracture below, situated a little to the left of the mid-line, he trephined. The dura just over the longitudinal sinus had been cut but not through. There was no hæmorrhage.

Probably in this case the damage was confined to the cortex and to that part of it which belongs to the left visual area above the calcarine fissure. The temporary loss of vision in the left lower quadrant was, I take it, due to the effects of shock on the corresponding part of the right lobe. From the position of the fracture, well above the inion, the occipital pole escaped. Central vision was retained (figs. 27 and 28).

Case 10.—*Entry.* In the mid-line of the occiput 1 in. from the inion.

Exit.—Large trephine opening in the left occipital region, with its centre $1\frac{1}{2}$ in. above and $2\frac{3}{4}$ in. behind the upper attachment of the left ear. There was a bulging septic hernia cerebri.

Nature of projectile.—? Rifle bullet.

Condition of wound.—Very septic.

X-ray examination.—Fracture of the skull between the entrance and exit wounds. There was no foreign body inside the cranium.

Operation.—On October 3, the holes in the occipital bone were joined up, very little bone being clipped away.

There has been a deep subcortical injury of the left occipital lobe, and in addition the wounds were very septic. Clinically, the patient had a right homonymous hemianopia which reached the fixation point. The charts show no dissociation between appreciation of movement and recognition of object, and there has been no recovery of vision in the eight months he has been under observation (figs. 29 and 30).

In each of these cases then there was destruction of the visual cortex, or of the optic radiations, or more commonly of both. It may be that in those cases in which no dissociation of the visual perceptions can be demonstrated, and in which no recovery of vision occurs, the damage has been extensively subcortical; but I cannot bring forward definite proof of this at present.

In Case 3, the position of the entry wound and the course of the bullet through the brain are of interest in view of the unusual visual symptoms he exhibited. The entry wound, in the case described by Smith and Holmes, was over the right supramarginal gyrus, and the exit over the left supramarginal gyrus, a little in front of the entry wound; so that they were both in the post-central regions of the brain.

In Captain de W. the bullet entered the brain in front of the left ascending frontal convolution and $1\frac{1}{4}$ in. from the nasio-inional line. Travelling backwards to the right occipital pole, it may or may not have injured the left optic radiation fibres; but it certainly passed through those of the right hemisphere. That his sensory symptoms corresponded in type to his visual defects is significant. In Smith and Holmes' case, sensation in the limbs was unimpaired, but he had bilateral motor apraxia as against the right-sided apraxia of Case 3. It is to be noted that in each case the bullet passed through both hemispheres.

Deductions can be drawn from several of the cases in support of the views of Holmes and Lister [4] and others on the cortical representation of the zones of the retina.

(1) Cases 6 and 7 supply evidence in favour of the contention of Holmes and Lister [4] that macular vision has its centre in the posterior or polar part of the visual areas. Further, since in cases in which the injury involves the apex of one occipital lobe the hemianopic line passes through the fixation point in the charts, and in those in which the polar region escapes central vision is retained, it seems

justifiable to conclude that the macula, like the rest of the retina, is not bilaterally represented in the cortex.

(2) The superior quadrants of each retina are represented in the upper, and the inferior quadrants in the lower part of each visual area.

(3) The periphery of the retina receives stimuli for the cortex of the anterior part of the area striata (Case 8).

Summary.

In reviewing the results of examination of cases showing visual defects from occipital injuries, I venture to bring forward the following conclusions:—

(*A*) With regard to the appreciation of movement when an object is oscillated in the so-called blind field.

(1) That movement should be given a place among the stimuli which are recognized as originating visual perceptions.

(2) That light and movement are the first stimuli to be appreciated in a recovering visual field. And since the appreciation of both returns *pari passu*, and since the field for light cannot be recorded on a chart, while that for movement can, the fields for movement, charted at intervals, give the earliest indications of recovering vision.

(3) That the presence of dissociation between the fields for appreciation of movement and recognition of an object afford a valuable aid in prognosis. In cases in which movement is perceived in the affected field, there will be some return of vision; on the other hand, where no movement is perceived after an interval of some months has elapsed the affected field will probably be permanently blind.

(4) That recovery for the appreciation of movement begins at the periphery of the field, and extends inwards toward central vision.

(*B*) That the types of visual dissociation exhibited are analogous to the dissociations of general somatic sense impressions described by Head and his co-workers as occurring from cerebral injuries.

(*C*) That in certain of the cases a consideration of the probable damage to the brain along with the charts of the visual fields yields facts which support the contentions of Holmes and Lister on cortical representation of the retina.

(1) That macular vision has its centre in the posterior part of the visual area.

(2) That the macula, like the rest of the retina, is not represented bilaterally in the cortex.

(3) That the cortical centre of the peripheral zones of the retina is in the anterior part of the area striata.

(4) That the superior quadrants of each retina are represented in the upper, and the inferior quadrants in the lower part of each visual area.

I must express my indebtedness to Dr. Collier, Dr. Buzzard, Dr. Guthrie, Dr. Head and Dr. Kinnier Wilson, for their kind advice, and for permission to use my notes on the patients under their care I have observed at the Empire Hospital for Officers. My grateful thanks are due to Dr. Fearnsides for his valuable criticism.

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PROGRESSIVE ATROPHY OF THE GLOBUS PALLIDUS.

(*Primary Atrophy of the Pallidal System.*)

A SYSTEM DISEASE OF THE PARALYSIS AGITANS TYPE, CHARACTERIZED BY ATROPHY OF THE MOTOR CELLS OF THE CORPUS STRIATUM.[1]

A Contribution to the Functions of the Corpus Striatum.

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New York.

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PART I.

Chapter I.—Introduction.

It is now a century since James Parkinson [92] wrote his celebrated essay on the "shaking palsy" and with the skill of a master outlined the chief clinical features of the disease which justly bears his name. There are few, if any, contributions to medical literature which excel in exactness of observation and clarity of expression Parkinson's original communication on paralysis agitans. Like

[1] Presented at a meeting of the American Neurological Association held in Washington, May 8, 1916.

Ménière's classical description, however, it was merely a clinical delineation, by means of which a certain group of cases could be readily recognized and differentiated. Ménière's disease in the course of time has been found to be dependent on a number of distinct pathological entities, and this I believe will be the fate of Parkinson's disease. In short, I would regard paralysis agitans as a syndrome, with a definite and characteristic complex of symptoms, which may be caused by a variety of pathological lesions.

Since Parkinson's time there have been many notable contributions to the symptomatology of this subject, as well as a vast amount of pathological research in an effort to find and identify the essential lesion of the disease. Many theories have been promulgated and a glance at the monographs of recent years will show the various and conflicting points of view, the great diversity of pathological findings, and the absence of any well defined and harmonious conception as to the true nature of this interesting malady. The theories, even of to-day, include such widely dissimilar structures as the cerebral cortex, cerebellum, basal ganglia, the brain-stem and the spinal cord. Even the glandular and myogenic conceptions are still upheld by some.

Clinically, three types of the disease are recognized, viz.: the *presenile* and *senile*, the *symptomatic*, and a rare *juvenile* form. There are also certain subdivisions corresponding to variations in the symptomatology; such as the paralysis agitans without tremor, the more rare paralysis agitans without rigidity, and various irregular or incomplete manifestations of the disease—*formes frustes*.

It is unlikely that an affection of this character, which is so diverse in its clinical manifestations, should have as its basis a uniform pathological lesion. The paralysis agitans group undoubtedly includes a variety of forms, which are related clinically as they present the chief symptoms of Parkinson's syndrome (rigidity and tremor), but which may be distinguished by differences in the localization and character of the underlying pathological lesions.

In brief, our position toward paralysis agitans to-day is much what it was toward spastic paralysis (paralysis with its associated spastic phenomena), before the function and course of the pyramidal tracts were known.

In the present study, an attempt is made to distinguish the juvenile form of paralysis agitans from the larger syndrome, on the basis of certain definite pathological changes in the motor cells of the corpus striatum, viz., *the globus pallidus mechanism*.

The juvenile type of paralysis agitans I would regard as a pure system disease, characterized by a slowly progressive atrophy of the motor neurones of the globus pallidus mechanism, while the paralysis agitans of later life, the presenile, senile and symptomatic forms are dependent upon senile and vascular degenerations in the course of this same mechanism. I believe that it is possible to differentiate the paralysis agitans group pathologically and to a certain extent clinically, precisely as in other organic affections of the central nervous system.

The progressive atrophy of the globus pallidus would therefore represent in the domain of the motor system of the corpus striatum the same pathological type as primary lateral sclerosis in the corticospinal motor system. The one is a primary atrophy of the pyramidal tract system, the other a primary atrophy of the efferent pallidal system.

The functions of the corpus striatum are still veiled in a certain mystery, notwithstanding the many notable contributions of recent years, and one has only to scan the list of syndromes ascribed to the striate body to obtain an idea of the inherent difficulties of this question and the conflicting symptomatology of this region. A system degeneration sharply limited to the motor neurones of the globus pallidus mechanism would therefore be an ideal lesion on which to construct a syndrome of the globus pallidus and should throw much light on the functions of this obscure neural mechanism.

In recent years there have been described two important syndromes of the corpus striatum, viz.: (1) The Vogt syndrome, characterized by spastic diplegia with athetosis and pseudo-bulbar palsy, the lesion in this group of cases being the *état marbré* limited to the caudate nucleus and the putamen (the neostriatum); and (2) Wilson's syndrome, based upon progressive lenticular degeneration, which is characterized by rigidity and tremor of the Parkinson type, dysarthria, and is associated with tonic and clonic spasms and occasionally athetoid movements. I shall attempt to reconcile these two syndromes and their points of difference in the chapters on the functions of the corpus striatum.

Evidence will also be presented for regarding the motor disturbances of paralysis agitans as one of the cardinal types of central paralysis.

This form of palsy is produced by disease of the motor or efferent system of the globus pallidus, which exercises a controlling influence upon the extra-pyramidal motor system. The large motor cells of the globus pallidus system occupy in the automatic motor nervous system the same position as the cells of Betz in the corticospinal system, the corpus striatum controlling automatic and associated movements,

while the higher cortical centres are concerned with isolated synergic movements.

Both of these motor systems in addition to their function of innervation also exercise a certain control or inhibition upon muscle tonus, so that a destructive lesion produces not only paralysis, but an increase of muscular tonus as well. Both types of central palsy are therefore associated with rigidity, and a paralysis of either produces a characteristic and distinctive symptomatology. A lesion of the pyramidal tract system is followed by the phenomena of spastic paralysis; a lesion of the pallidal system by the phenomena of paralysis agitans.

Chapter II.—Report of Clinical Cases.[1] (Personal Observations.)

This chapter includes the clinical reports of four cases of paralysis agitans beginning in the second and third decades of life, viz., the thirteenth year, fifteenth year, twenty-sixth year and thirtieth year. The autopsy and histological findings in Case 1 are described in Chapter IV.

Case 1.—*Clinical diagnosis:* Paralysis agitans (juvenile type). *Pathological diagnosis:* Progressive atrophy of the globus pallidus.

Summary: Tremor and rigidity of the paralysis agitans type beginning at the age of fifteen years, onset with rhythmical tremor of the left foot and hand followed by progressive weakness and rigidity. Later, similar involvement of the opposite side, with typical attitude, facial expression and propulsive gait. At the age of twenty, there was dysarthria, tremor of the face, tongue and eyes. Gradual but steady progression of the disease terminating in complete muscular rigidity with anarthria. Death at the age of 40 *from exhaustion and heart failure. For report of autopsy and histological findings see Chapter IV.*

History.—The patient, W. H., a Hebrew, was admitted to the neurological wards of the Montefiore Hospital on February 20, 1893, at the age of 17. He remained in this institution, and was under continuous medical observation until his death, which occurred at the age of 40. The family history so far as known was negative; his parents, brothers and sisters, are all alive and well. No other members of the family have had any disease remotely resembling that from which he suffers. In early childhood, on one or two occasions he is said to have had convulsions, but has never had any seizures since the infantile period. At the age of 5 years he had a rather severe fall,

[1] Cases 1 and 2 are from my beds in the neurological wards of the Montefiore Hospital: Case 3 is from the Third Division of the New York Neurological Institute.

but recovered completely and apparently suffered no untoward after effects. He contracted gonorrhœa in early youth, but denied any syphilitic infection. He was a bright, intelligent boy, attended school and developed like other children up to the age of 15, when the first symptoms of paralysis agitans made their appearance. It is perhaps of interest to note that even in early childhood a certain motor disturbance or inadequacy may have been present: he was said to have always been awkward in climbing fences, jumping onto

FIG. 1. *Case* 1.—Progressive atrophy of the globus pallidus at the age of 17, two years after the onset of the disease. Note the attitude, position of hands and fingers, and the well-defined contour of the muscles (rigidity). [From Dr. Wiener's Report.]

wagons, &c., and was never so agile in this respect as other boys. He was also backward in writing because he could not learn to write quickly enough although in other respects he stood well in his classes. He also stated that the boys used to call him "false face," referring to a peculiarity of facial expression. He thought, too, that his speech was not so good as it should have been. These earlier signs of the disease may or may not have been present, although his statements were corroborated by the mother, but it is

certain that quite definite symptoms of paralysis agitans made their appearance at the early age of 15 years.

The first symptom was a tremor of the left foot, which at the time was attributed to a fall from a wagon by which the left ankle was sprained. This tremor gradually increased in severity and subsequently made its appearance in the left hand and arm, both the arm and leg becoming gradually weaker and stiffer. A year later the extremities on the right side became similarly affected and in the same order, first the leg and then the arm. During the next few years the disease made gradual progress, and, in five years from the time of onset, articulation and deglutition were definitely disturbed. There was no history of burning pain, heat or excessive sweating, but simply the gradual extension of tremor and rigidity, first on the left side, subsequently on the right, and later involving the muscles of the face, tongue and throat.

The original physical examination on admission to the hospital in 1893 was made by Dr. Joseph Fraenkel, and reads as follows (see fig. 1): The facial expression is stolid and mask-like. There is a tremor of the eyes in looking to the right and left (nystagmus), which is accompanied by clonic twitchings of the eyelids. The ocular excursions are normal in all directions, except for the tremor accompaniment. Facial movements are present but diminished, and are accompanied by tremors of the *orbicularis oculi et oris*. The tongue is protruded slowly, and there is a marked lingual tremor. The voluntary innervation of the soft palate is diminished, but is quite active when stimulated reflexly. The pupils are equal and react promptly to light and accommodation. On standing, the attitude is bent and the extremities are somewhat flexed and the seat of coarse rhythmical tremors. The hands are fixed in the typical position, flexed at the metacarpo-phalangeal articulation, the phalanges being extended and the thumb adducted (fig. 2). The muscles are fixed and rigid, and resist passive movements. The mechanical irritability of the muscles is normal and the electrical reactions show no qualitative change. The tremor is greatly increased by excitement and persists during rest. It is diminished or ceases on any intentional movements. It ceases entirely during sleep. The tendon reflexes of the upper extremities are diminished and difficult to elicit. The patellar reflex is active, as is also the ankle-jerk, and at times an inconstant ankle clonus is elicited (pseudo-clonus). The abdominal reflexes are lively; the cremasteric reflexes are not elicited probably owing to scars, the result of a gangrenous intertrigo. In the ward the patient remains seated practically all of the time and makes no attempt to change his position. If requested to walk, the universal tremor immediately becomes emphasized; he rises with difficulty, stands on the tips of his toes with arms and legs in flexion, and after a considerable interval begins to walk with short steps on the tips of his toes, which increase in rapidity until a well-marked propulsion develops.

Every movement is performed slowly and with the appearance of great deliberation. If he is told to rise from a sitting posture, a long interval of many minutes elapses before the command is translated into motion.

All sensations are normal, and there are no sphincter troubles. There is

no defect or retardation of the intelligence. The speech is monotonous, nasal, and often unintelligible, so great is the dysarthria. The mouth has to be opened forcibly to examine the throat on account of the muscular rigidity.

The heart, lungs, and abdominal viscera are normal. The urine has a specific gravity of 1010, is acid and free from albumen or sugar.

Dr. Fraenkel at this time was inclined to regard the case as a combined form of paralysis agitans and multiple sclerosis.

FIG. 2. *Case* 1.—At the age of 25, showing facial expression and contractural deformity of the hands.

This patient remained in the Montefiore Home during the next twenty years of his life and awakened more than usual interest, because of his youth and the evident Parkinsonian features of his malady. He was examined on various occasions by Dr. Dana, Dr. Sachs, and Dr. Collins, and it was generally agreed that the clinical picture corresponded very closely to that of paralysis agitans. The universal and severe tremor, however, was a source of some confusion and at times a relationship to multiple sclerosis was seriously

considered. The case was recorded many years ago by Dr. Wiener [75] as one of paralysis agitans, and about the same time by Dr. Sachs [68] as a combined form of paralysis agitans and multiple sclerosis.

The patient first came under my personal observation when he was 25 years of age, and during the remaining fifteen years of his life I had many opportunities for the study of this unusual case. The clinical picture remained in its essential features the same, with, however, a very gradual progression of all the symptoms.

FIG. 3. *Case* 1.—At the age of 31. Note the fixed smile, the bright intelligent eyes and the Parkinsonian deformities of the hands and fingers.

There was the typical facies of advanced paralysis agitans, viz., a fixed, immobile expression with infrequent winking and but slight power of voluntary movement. The bright observant eyes were in marked contrast to the mask-like expression of face. Under the influence of a pleasurable emotion his face would gradually assume the expression of smiling, which would linger for a time and then gradually fade away (fig. 3). Marked rhythmical tremors of the lips, eyes, eyelids, and tongue, which increased under excitement and effort: the typical Parkinsonian attitude and gait with coarse rhythmical

tremors which increased during excitement or the first efforts at movement, but diminished when the movement was well under way. There was the pill-rolling movement of the fingers and an increase of the tremor, or its appearance in some other portion of the body if suppressed in an arm or leg. The tremor was rhythmical in character, registering from six to eight vibrations a minute, which under excitement would increase in celerity. It had never at any time the ataxic character of the intention tremor of multiple sclerosis. The nystagmus movements of the eyeballs resembled in time and quality the general tremor and were evidently of similar nature. The gait and station, the slowness of movement, the deficiency of motor initiative, the infrequent winking, the rigidity and flexion contractures of the extremities were all characteristic of the paralysis agitans syndrome.

The knee-jerks and Achillis jerks remained moderately active, while the tendon reflexes of the arms were diminished or difficult to elicit. The abdominal reflexes were constantly present, until a late stage of the disease when they were frequently masked by the board-like contractions of the abdominal muscles. There were no associated movements and no tendency to involuntary muscular spasm or athetoid movements.

The plantar reflex usually yielded a flexor response. At times an apparent extensor response (Babinski) was obtained, but this was not typical and almost always disappeared if the leg was flexed at the knee, and the reflex tested in this position. I regarded this phenomenon as a pseudo-Babinski, associated with the contractural conditions of the muscles.

At times during an examination there would occur mild emotional reactions, sometimes laughing, sometimes crying; these however had not the forced spasmodic character of a true pseudo-bulbar affection.

Passive movements of the extremities met with great resistance on account of the rigidity, and there were those peculiar tremor or wave-like interruptions of the movement (cog-wheel symptom) which are so characteristic of the rigidity of Parkinson's disease. The contour of the muscles was well marked and the muscle bulk was well preserved. The myotatic irritability was normal. The sensations were always normal in every detail—touch, pain, temperature, and the deep sensibility, vibration and the articular sense.

The intelligence was essentially intact. There was, however, present that peculiar contraction of the mental horizon and slight gradual deterioration which so frequently accompany chronic incurable affections.

The eye-grounds were normal, and the Wassermann test was negative in the blood and cerebrospinal fluid.

Note of Examination, December 14, 1913.

The patient is perfectly rigid from head to foot. The muscular rigidity now predominates, there being very little spontaneous tremor, which is in marked contrast to the generalized tremor of the first ten years of the disease. The facial expression is one of fixed immobility, and the head is bent forward on the chest and fixed by the rigid contraction of the neck

muscles. The mouth is held open with the lips separated and there is a constant dribbling of saliva over the chin (sialorrhœa). Much of the time the eyelids are held closed.

If asked a question the only response is a tremulous flicker of the eyelids and of the lips; occasionally, after great effort and a considerable interval of time, a gurgling throat sound is emitted, but nothing approaching the semblance of a word. There is complete anarthria. While sitting in a chair there is no spontaneous movement, save an occasional tremor of the hands and sometimes of the arms.

On direct fixation of an object with the eyes there is no nystagmus, but on following the object to the left or right a slow rhythmical ocular tremor is apparent in the extreme position. There is no evidence of ocular palsy. The jaws cannot be separated very widely because of muscular spasm, and there is a slight tendency to masseter tremor. The movement of closing the jaws is very feeble. The tongue can be protruded very slowly, and during the movement there are quick rhythmical tremor-like movements remotely suggesting that of the tongue of a snake. The eyelids can be closed, but the movement is weak and the contractions are not firm. The pupils are equal and react promptly both to light and accommodation. The soft palate is somewhat difficult to see, and there is but little movement on voluntary innervation. The palatal reflex is preserved and the gagging reflex is quite active.

The patient is able to swallow soft and liquid nourishment, and seems to relish his feedings. Much, however, is lost by a return through the mouth, but very seldom by the nose if carefully fed, and curiously enough there is seldom any coughing from deflection of the food into the larynx. I watched him feeding on various occasions and was surprised to note the ease with which nourishment was taken, considering the extensive and grave involvement of the bulbar muscles.

The left hand and arm are rigid and in a state of contraction, which is fixed and cannot be overcome. The fingers and thumb are in the attitude characteristic of Parkinson's disease, still retaining the essential elements of the interosseous position. There is very slight voluntary power of flexion of the elbow, wrist, and fingers, and during such movements there is an increase of the rhythmical tremor. The right arm and hand are in practically the same state of weakness and rigidity, and also the seat of rhythmical tremors, which increase during excitement and attempted movements. There are no evidences of associated movements in the upper extremities. The legs are in a state of massive rigidity, flexed at the knees and with practically no power of voluntary movement.

The muscles of the abdomen are firm and boardlike, and as a result no abdominal or epigastric reflexes can be elicited. The plantar reflexes are inactive and are usually of the flexor type. Occasionally an apparent extensor response is obtained, but this is inconstant and changes to flexion, especially if the muscles of the legs are relaxed at the knee. The Babinski phenomenon is

therefore absent. I became convinced after many examinations that this was not a true Babinski reflex, but a pseudo-phenomenon induced by muscle rigidity and spasm.

If turned or lifted to his feet, his body moves as a solid block, and I can recall no case in which the general bodily rigidity and fixation has been more extreme. He is almost as inert as a marble statue, with the exception of the rhythmical tremor, which is always slightly present and is exaggerated from time to time.

The tendon reflexes of the arms are present and not exaggerated. There is no trace of periosteal reflexes or undue exaggeration of the tendon jerks. The masseter reflex is present (jaw-jerk). The knee-jerks are present, active, but not exaggerated, and both Achillis jerks are present. There is no ankle clonus or wrist clonus. The myotatic irritability and idiomuscular reaction of the muscles of the arms and legs are normal.

During the examination the patient had occasional emotional outbursts of laughing or crying, but without the corresponding range of facial expression such as would be observed in a true spastic case of pseudo-bulbar palsy.

He is said to have an excessive appetite and sleeps a great deal during the day. The sphincters are under good control. A detailed sensory examination was not possible; however, he felt pinpricks as a painful sensation in the various segments on both sides of the body. There was well-marked dermographia.

It is difficult to speak with much certainty of the degree of intelligence of a human being who is immobile, speechless, and without facial expression. That there had been through the years of chronic invalidism a gradual deterioration of the higher qualities of mind was certain. There was, however, no gross alteration of the mental processes; no delusions, hallucinations, or loss of memory, and the defect was not greater than might be expected after years of paralysis, dysarthria, and the resulting social isolation.

The outline of the liver anteriorly was difficult to demarcate because of distension and tympany of the colon; posteriorly its boundaries were normal. The patient gradually became weaker, and a little over a month subsequent to the above examination he succumbed to exhaustion and heart failure. Death, January 28, 1914.

This case is remarkable on account of the early age of onset, 15 years, and the rapid progression of the symptoms. That there should be considerable involvement of the bulbar muscles within a period of five years is also somewhat unusual. From the statements of the patient, also corroborated by the mother, it would appear that certain prodromal symptoms, e.g., facial immobility and a certain awkwardness of movement, were already noticeable in early childhood, long before the appearance of the tremor. For this we are dependent merely upon their statements, but it is suggestive and not at all improb-

able, and the existence of such prodromal symptoms should be carefully investigated in subsequent cases. There was no history of the occurrence of any similar disease in other members of the family, although a familial incidence is by no means infrequent in the juvenile type of the disease.

The tremor and rigidity began on the left side, first appearing in the foot and then the arm. A year later similar symptoms were manifested on the opposite side. The tremor and rigidity were both characteristic of paralysis agitans. In the earlier years of the disease the tremor was coarse and almost universal, involving even the face, tongue and eyes, and was at times violent, more especially under the stress of emotion or attempted movement. During actual movement, however, the tremor would diminish, and usually ceased as the hand approached an object, in this respect differing essentially from the tremor of multiple sclerosis. It was, therefore, not an intention tremor. There was also a nystagmus-like tremor of the eyeballs, which, however, partook of the nature of the general tremor and did not have the characteristics of a true nystagmus. I regarded it as a tremor oculi, and a pseudo-, not a true, nystagmus. At one period of the disease the tendon reflexes of the lower extremities were active and there was even a tendency to ankle clonus, which, however, was not constant and was closely related to the tremor. This again was a tremor or pseudo-clonus and not the true clonus of spasticity.

The early age of the onset of the disease, the marked general coarse tremors, the pseudo-nystagmus and the pseudo-clonus in the earlier years of observation, gave rise to the suspicion of a multiple sclerosis of paralysis agitans type, or at least a combination of the two diseases. During the subsequent course of the malady, however, such a combination could be definitely excluded, and the case for many years had been regarded as a juvenile type of paralysis agitans. After the publication of Wilson's monograph on Lenticular Degeneration the case was again studied with renewed interest, having in mind the possibility of a chronic type of this affection which had become stationary. Against this view was the chronicity and long duration of the malady, the absence of emaciation, the absence of choreiform and athetoid movements, or the other active spasmodic manifestations of Wilson's disease, and the absence of mental symptoms. As involvement of the pyramidal tracts could be definitely excluded, the clinical diagnosis of paralysis agitans of the juvenile type seemed to be clearly established. A complete autopsy and histological examination of the central nervous

system was made in this case, which is, I believe, the first of its kind to be recorded in medical literature (see Chapter IV).

Case 2.—*Clinical diagnosis:* Paralysis agitans (juvenile type).

Summary.—Tremor and rigidity of the paralysis agitans type beginning at the age of 13 *years. A woman, aged* 33, *presenting the typical clinical picture of paralysis agitans, viz., rhythmical tremors and progressive rigidity. Onset of the disease in the right arm at the age of* 13, *later extending to the left and then the lower extremities. Speech and deglutition were affected. There was the Parkinsonian mask and attitude, infrequent winking, propulsion and the slowness of movement characteristic of that disease.*

History.—The patient, E. I., at the time of writing (1916) was aged 33. She was admitted to the Montefiore Home and Hospital in August, 1912, and since that time she had been under continuous observation in the neurological wards of that institution. She was born in Russia, of Jewish parentage. Her father and mother were alive and in good health and were first cousins. There were six children in all, three boys and three girls, and all except the patient enjoyed good health. So far as known there was no history of any similar affection in the family.

The patient was the eldest of the family and the circumstances of her birth were entirely normal. She was breast fed until over a year old. There were no convulsions in infancy or subsequently. Her first menstruation made its appearance at 11 years of age, and for a year recurred every two weeks. Since that time the interval had been normal and the duration of the flow about four days. At times there was dysmenorrhœa. She attended school, was bright and attentive, and there was at no time any suggestion of mental retardation. In early childhood she had measles, but otherwise escaped the usual infections of that period and had no other illnesses.

History of the Disease.

The malady from which she suffered began when she was 13 years of age, with a tremor of the right hand, which was aggravated on attempting any movement. This gradually increased and extended up the arm, and one year later the left arm was similarly affected. For two years the symptoms were limited to the upper extremities, after which, at the age of 15, there developed a certain weakness and stiffness of the left leg, so that she walked with a limp and the left leg trembled under her on standing. At the sixteenth year the right leg was similarly affected. She continued, however, to assist her mother in certain household duties up to the seventeenth year, and was quite capable of feeding herself and even carrying a glass of water to the lips without spilling it.

The tremor and weakness of the extremities gradually increased in severity after this age, but she continued to walk without assistance up to her twentieth

year. After this age it was very difficult for her to rise from a sitting posture without assistance and she could walk only if supported. She stated that since her seventeenth year there had been a tendency to tremor of the lips and eyelids. After the twenty-third year she had experienced some difficulty in swallowing liquids, and unless she was careful there was a tendency to regurgitation through the nose. For about the same period of time the speech had

FIG. 4. *Case* 2.—Juvenile paralysis agitans at the age of 29; onset of the disease at 13; showing the mask-like expression of the face in repose.

been low pitched, measured and somewhat dysarthric. There had been no diplopia, no visual disturbance, no history of sphincteric trouble, and at no time paræsthesiæ, nor did she complain of sweats, excessive heat or burning sensations. She had been quite free from pain during the early years of her malady, and only in recent years since the rigidity had become generalized was there a tendency to moderate aching pains in the spine. During the earlier

period of her malady she suffered occasionally from headaches, but these had rarely recurred during the years of observation at the home. The headaches were unaccompanied by vomiting or vertiginous seizures.

Physical examination (August, 1912, at the age of 29): She is of medium size, well nourished and has a good colour. The facial expression is fixed and mask-like, but the eyes were alert and express intelligence. Occasionally her face breaks into a sort of stiff smile, which comes quickly and fades away slowly (figs. 4 and 5).

FIG. 5. *Case* 2.—Note the slow lingering smile and the bright intelligent eyes.

The speech is slow, low pitched and monotonous and one has to listen intently to understand. The pupils are equal and react promptly to light and accommodation; the ocular excursions are normal in all directions, but the lateral movements, and in a lesser degree the vertical, are accompanied by rhythmical tremors of the eyeballs. This does not appear on fixation of an object, but only during the movements of the eyes to the right or left. In the

extreme position when the eyes fixed the object intently it diminished or ceased. On closing the eyes there is a marked tremor of the eyelids.

The voluntary movements of the facial muscles are diminished and she is unable to wrinkle the forehead by innervating the frontalis muscle. Frequently during the examination the face becomes flushed with excitement. The winking reflex is very infrequent, which contributes to the mask-like fixation of the face. She has had no attacks of forced laughter or weeping, and although she is very prone to smile this is an indication of a good disposition and is not of the nature of a forced emotional discharge. There is an abundant growth of hair about the upper lip and chin (hirsuties). Her teeth are well preserved and in good condition. The tongue is protruded in the median line and is very tremulous. The voluntary and reflex innervation of the palate is normal. Both sterno-cleido-mastoid muscles stand out prominently in the recumbent position owing to rigidity.

At rest there is a constant rhythmical tremor of the fingers, hands and forearms. This varies in intensity and when quiet and unobserved it practically ceases, but observation, any excitement or attempted movement produces an immediate exaggeration and generalization of the tremor, which appears in the face, head and legs. Usually at rest there is some tremor of the legs, especially of the feet and toes. The tremor is slow, ranging from four to six vibrations a second, but its rate and amplitude increase under excitement.

If the attempt is made to place the index finger on the tip of the nose, there is an interval of inaction before the movement is started, during which there is an increase of the tremor; this increase continues during the early portion of the motor excursion, but gradually diminishes as the objective of the intended movement is reached, when the tremor ceases entirely. It is, therefore, in no sense an intentional tremor, as this term is used to express the tremor of multiple sclerosis, although there is a distinct exacerbation of the tremor during movement. There is a similar recrudescence of the tremor during the return movement of the arm, which diminishes or may cease when the extremity has returned to its former position.

The muscles of the arms and legs are rigid, and offer considerable resistance to passive movements. The musculature is well developed, and the contour of the more prominent muscles stands out sharply. If passive movements of the extremities are made, there is a marked resistance, but the flexion contractures which are present in the arms and legs may be overcome by strong pressure, so that there are no fixed or permanent contractures.

The hands and fingers are held in a modification of the interosseous position, flexion of the basal with extension of the distal phalanges and the thumb held in adduction beneath the fingers. The feet are in equinovarus, with a tendency to hyperextension of the great toes. She is unable to lift either leg from the bed, but can flex the knees and hips slowly, and with great effort. The arms can be moved at the shoulders and the elbows, but there is little power of voluntary movement in the hands or fingers.

The tendon reflexes are all present and rather active; viz., the jaw-jerk,

the supinator, biceps and triceps reflexes, the knee-jerks and the Achillis jerks. There is also a tendency to clonus in the lower extremities, but this is inconstant—a pseudo-clonus—and is closely related to the tremor disturbance. There is no exaggeration of the periosteal reflexes. The abdominal reflexes are present and equal on the two sides, and the plantar reflex is of the flexor type. At times an apparent Babinski response is obtained, but this is a spurious or pseudo-extensor reflex, and disappears promptly if the knee is flexed. It is associated with the tendency to a fixed dorsal position of the great toe when the leg is extended, and is probably dependent upon muscle rigidity.

The general sensibility is perfectly normal to touch, pain, and temperature; the articular sense and the vibration sense are also normal. The sense of smell and taste are preserved. The visual fields are normal, and hearing is equal on the two sides and of normal acuity.

The heart and lungs are normal, and the abdominal viscera so far as could be determined by palpation and percussion are normal. Special attention was given to the area of hepatic dulness, which was normal. The urine is alkaline, specific gravity 1012, and is free from albumen, sugar and casts.

December 17, 1913. — At rest in the recumbent position there is a slight tremor only of the right hand and forearm. She states that there is considerable variation in spontaneous tremor from day to day, as well as the degree of rigidity. Some days her muscles are much more relaxed than others.

On attempting to speak, there is tremor of the facial muscles and an immediate reappearance of the tremor of the arms and body. The ocular excursions take place in all directions, with the exception of the movement of convergence, which is but poorly developed. On looking to the right and left, there is a slow rhythmical oscillation of the eyeballs (tremor oculi). The face is without expression and rather rigid in appearance, with a tendency to pointing of the lips. The stolidity of expression is also manifested on emotional innervation (a smile), there being only a lighting up of the expression of the eyes and a transverse movement of the angles of the mouth, which fades away gradually. Winking occurs at long intervals only, and is slower than normal. There is no tendency to emotional innervation of an explosive nature, but she flushes very readily during the examination.

The general rigidity of the body and extremities is as noted in the previous examination. On making passive movements of the arms the so-called cog-wheel resistance or wave-like interruption of the flow of the movement is observed. Any attempt to move the arms is the signal for a general exacerbation of the tremor, which increases for a time during the course of the movement, but diminishes or ceases when it reaches its termination. The legs are rigid, and resist passive movements, as do the arms, and a cog-wheel resistance similar to that of the upper extremities is noted. Voluntary movements of the legs are very slow, and very slight in degree, and are accompanied by coarse rhythmical tremors. The right leg is a little weaker than the left. The abdominal muscles are firm and rigid. On the right side a distinct abdominal reflex can be elicited, which is faintly present on the left.

Movements of the head are slow and restricted, and are associated with tremor. The movements of the lower jaw and palate take place slowly, and without tremor. There is, however, a well-marked tremor of the tongue during protrusion.

She is able to stand on a narrow base without assistance, but must first be lifted into the standing posture. Closure of the eyes produces no disturbance

FIG. 6. *Case* 2.—At the age of 33. Lateral view, showing posture and the general muscular rigidity.

of the equilibrium. She stands bent forward, the head bowed and the legs and arms slightly flexed in the typical attitude of Parkinson's disease (figs. 6 and 7). On turning round, she moves in a solid piece, and immediately becomes stationary again. She is able to take a few short steps forward, walking on the ball of the foot, but soon develops propulsion. On attempting to walk backward, she soon loses her balance and falls in a solid piece without any

associated movements of the extremities as would naturally be made to recover equilibrium.

The plantar reflexes are diminished, and are usually of the flexor type. Occasionally an apparent extension of the great toe is obtained, but only when the knee is extended and the great toe naturally tends to hyperextension. If the leg is flexed at the knee and the reflex is then tested, flexion of the toes

FIG. 7. *Case 2.*—Anterior view. Note the flexion attitude, the deformities of the hands and fingers and the prominence of the tendons of the sterno-cleido-mastoid muscles.

almost invariably results. The Babinski reflex is therefore not present. The tendon reflexes of the arms are feeble, and can scarcely be elicited. There is no exaggeration of the periosteal reflexes. The knee-jerks are exaggerated; the Achillis reflexes are present, equal, and not exaggerated. There is no patellar or ankle clonus. There are no associated movements during volitional acts as in ordinary hemiplegia.

Her intelligence is undisturbed. She is quiet, good-natured, and always cheerful, and shows no mental defects of any kind.

March 19, 1915.—The menses are perfectly regular, and her general health and strength are fair. She has a good colour. There is no loss of flesh or emaciation, and no elevation of temperature. The speech is less distinct, low-pitched, and quite toneless. The tongue is protruded promptly, and, while moving forward, there develops a curious tremor somewhat suggestive of the darting of a serpent's tongue. The pupils are moderately dilated, and react promptly to light. There is no power of convergence and very little response on accommodation. The abdominal reflexes are either not elicited, or the response is very faint, owing to rigidity of the abdominal walls. There is no ankle clonus and no patellar clonus, and the plantar reflex is variable due to permanent spasm of the extensor hallucis longus. If the knee is flexed which relaxes this spasm the plantar reflex is almost constantly of the flexor type. The voluntary innervation of the soft palate is diminished, but, on reflex stimulation, a prompt reaction and gagging reflex is produced.

April 16, 1915.—Plantar reflex is as noted in many previous examinations, i.e., variable with the leg extended, sometimes flexor, sometimes an extensor response. With the knee relaxed, the reflex is almost always flexor. There is a tendency to permanent fixation of the great toe in extension. The suggestion of a Babinski reflex is, therefore, not a true reflex, but a spurious phenomenon.

She swallows without difficulty solid food, but liquids occasionally regurgitate and cause coughing. Lying in bed with the head supported on a pillow, the sternomastoids stand out prominently from permanent rigidity. The tremors of the face, eyelids, tongue, head, arms and legs are as noted in previous examination.

There is very little spontaneous tremor unless excited by questions or observation and especially by any motor activity. Any movement is performed slowly and with great effort. There is usually a considerable interval after the command is given to move an extremity before it is put into effect. Usually she declares first that she cannot do it and has to be urged. With the movement there develop coarse rhythmical tremors which cease after the arm is lifted to its object. It is therefore an action tremor and not an intention tremor in the sense in which this term is used in disseminated sclerosis.

The general rigidity is the same as at previous examinations and is increasing. The spinal muscles are fixed and rigid, so that in the recumbent posture it is possible to slip with ease the hand into the concavity beneath the spine.

The optic discs are normal. There has been no disturbance of the sphincters and no sensory disturbances, either subjective or objective. At no time has there been noted any choreiform, athetoid or spontaneous spasmodic movements, only the rigidity and tremor.

The Wassermann test of the blood and cerebrospinal fluid was negative. There was no increase of cells or globulin.

This case is identical in its course and symptomatology with Case 1, and presents the cardinal symptoms of paralysis agitans beginning in

very early life, viz., the thirteenth year. There was no history of any familial tendency to such an affection, nor were there manifested any of those latent or prodromal symptoms which seem to have preceded the disease in Case 1. It is, however, interesting to note the consanguinity of the parents, which is so frequently encountered in other system and degenerative affections of the central nervous system.

The clinical picture consisted of a generalized tremor involving all four extremities, the face, eyes, eyelids and tongue, associated with progressive rigidity of the muscles. There was the typical gait and attitude, the mask-like expression of the face and a well-marked dysarthria and dysphagia, which came on comparatively early in the disease. The tremor was rhythmical in character and was greatly exaggerated by the first attempts at movement, but as the hand gradually reached its object the tremor movement lessened and eventually ceased. Then, as the arm was slowly withdrawn, the tremor returned with violence, gradually diminishing as the arm reached its original posture.

In this patient, as in Case 1, the tremor tended to diminish as the rigidity increased. Both tremor and rigidity had the characteristic features of paralysis agitans. The tremor was rhythmical, usually from four to six vibrations a second; if checked voluntarily in one part it would reappear in another. The rhythm was synchronous in all of the parts affected. It ceased during sleep, and was always present in some degree during rest. The tremor of the eyeballs was for a time regarded as nystagmus, but subsequent and repeated observations demonstrated its relationship to the general tremor. The intelligence and sensations of the patient were normal and the only symptoms were those of the progressive motor disturbance, viz.: paralysis, rigidity and tremor. An affection of the pyramidal tracts could be definitely excluded by the absence of the usual accompaniments of the spastic paralysis.

Case 3.—

Summary.—Onset, with tremor of the paralysis agitans type, at the age of 26. *Gradual progression until all four extremities were affected. Typical posture of the hands and arms in standing and walking. Parkinsonian facies with infrequency of the winking reflex. No muscular rigidity, but the contour of muscles was prominent.*

History.—The patient was a man, aged 30, of Irish extraction, a labourer by occupation. He was admitted to the Neurological Institute (under the care of Dr. Bailey) on February 1, 1916, and gave the following history. There is no known familial tendency to tremor or other nervous disease.

He has always been moderate in the use of alcohol and tobacco. Eight years ago he acquired syphilis and received three years' continuous treatment with mercury and potassium iodide, which also included five intravenous injections of salvarsan at intervals of three weeks. He states that coincident with the appearance of the chancre there was a moderate jaundice, which was, however, merely transitory in character. He has had no shock or injuries, and is unable to assign any cause for the tremor which first made its appearance three and a half years ago at the age of 26. The tremor began in the right hand and progressed, gradually involving the entire right upper extremity. Two years later the tremor also appeared in the lower extremities. When the tremor was severe there was difficulty in articulation; this was however only transitory and was a part of the tremor. The left arm is also slightly involved, but in a lesser degree. The tremor is slow, rather coarse and quite rhythmical, ranging from four to five vibrations a second. The rhythm of the tremor is the same in all the extremities. It is very much exaggerated by any mental excitement and by observation. He states that on waking in the morning he is comparatively free, and at times even entirely free, from tremor. It makes its appearance after he has been up two or three hours and lasts during the remainder of the day, usually progressing as the day goes on. It becomes very coarse and violent under excitement, or if an effort is made to control it. While taking his history, he would rise and pace up and down the room, and this seemed to relieve somewhat the paroxysm tremor. The tremor diminishes or may cease entirely during an intention movement, and he is able to lift a glass of water to the lips without spilling, and shaves himself every morning without difficulty, using an ordinary razor. Since the onset of the tremor there is a marked tendency to hyperidrosis in hot weather. He perspires very freely and this manifestation is generalized and not confined to any one extremity. He complains of no pains and no paræsthesiæ. During sleep all tremor movements cease. The tremor is not relieved by taking alcohol, but diminishes considerably during treatment with hyoscin. There is no sensation of stiffness of the muscles, nor any disturbance of the gait, other than that produced by the tremor. He has been quite free from pain or other subjective sensations, e.g., heat or burning. There has been a complete freedom from headaches, vertigo, visual disturbances or other cerebral symptoms. His mind is perfectly clear. The sphincters are normal.

Physical examination, May, 1916.—The patient is above medium height, well developed, and presents no external evidences of a premature senility. The facial expression is rather fixed and staring, and it is noticeable that the winking reflex is quite infrequent, this reflex taking place only at intervals of from one to three minutes. The general posture, manner of holding the arms and hands, and the expression of the face are very suggestive of Parkinson's disease (fig. 8). There is no well-defined Parkinsonian mask, but the face is distinctly lacking in mobility of expression. The positions assumed by the tremulous hands, especially the right, are quite typical. On walking, it is

noticeable that he holds the right arm stiffly and to a lesser extent the left, and the arms do not participate in the natural associated movements which normally accompany this act. There is no demonstrable rigidity of the muscles. On making passive movements the so-called cog-wheel symptom of the upper extremities is suggested, but is not characteristic of Parkinson's

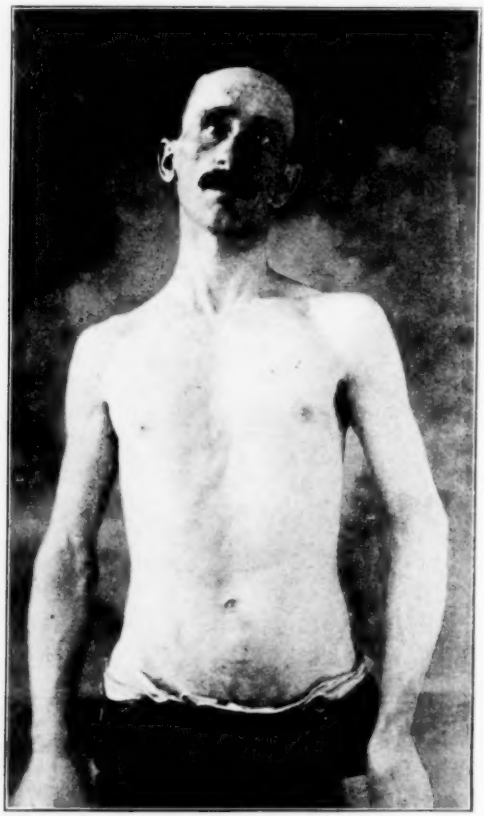

FIG. 8. *Case* 3.—Paralysis agitans without rigidity, beginning at the age of 26.

disease. While there is no hypertonicity of the muscles there is on the other hand no evidence of hypotonia, and the bodies of the muscles stand out quite distinctly under the skin. There is no diminution in the gross motor power. The tendon reflexes of both the upper and lower extremities are normal and equal on the two sides. The pupils are equal and react promptly to light and accommodation. The cranial nerves are normal. The outlines of the optic

discs are clear, and there is no evidence of neuritis. All skin reflexes, including the plantar, cremasteric, abdominal and sympathetic reflexes are present and normal. There is no disturbance of sensibility.

The speech shows a slightly tremulous character, but is otherwise normal. The special senses are undisturbed. The heart action is normal—no murmurs, and no hypertrophy. The systolic blood-pressure is 130. The general visceral examination is negative, save for a left inguinal hernia. The urine is negative and the Wassermann test of the blood and cerebrospinal fluid is also negative. (He stated that an examination of the blood some months before had shown a positive reaction.) There is no excess of globulin and no pleocytosis of the cerebrospinal fluid.

October, 1916. A subsequent examination on October 26, 1916, confirmed the previous observations. The tremor is slow, coarse and rhythmical, at times even violent, and involves the arms, especially the right, both lower extremities, and to a moderate degree the muscles of articulation. The facial expression is more stolid than at the previous examination, and a slight mask-like character is now quite evident. The attitude, especially of the hands and arms, is distinctly Parkinsonian. The winking reflex is very infrequent. Since the advent of cooler weather the tendency to hyperidrosis has entirely ceased. The muscles, especially of the arms and shoulders, present a wax-like prominence of outline, but there is no definite rigidity on making passive movements. He complained of a "heaviness" of the left leg in walking, but there are no signs of weakness or rigidity.

The pupils are equal and react promptly. All the skin and tendon reflexes are normal. All sensations, special and general, are quite normal. There is no complaint of subjective sensation of heat, burning or pain. The loss of associated movements of the arms in walking is quite evident, otherwise the gait is normal.

This case is of interest because of the early age of onset (twenty-sixth year), the history of an antecedent syphilitic infection and certain clinical features of the disease, viz., the absence of rigidity.

Paralysis agitans beginning in the third decade of life is probably of of the same type clinically and pathologically as the earlier juvenile cases, *e.g.*, Cases 1 and 2. Certainly in this patient there were no evidences of senility or cardiovascular degeneration which would justify classification with the senile group of this affection.

The possible relationship of syphilis in the etiology is interesting, but is merely speculative. There were no general cerebral symptoms preceding the disease ; it began insidiously and progressed gradually as is usual in paralysis agitans, and active antisyphilitic treatment had had no effect in checking the course of the disease.

The *tremor form* of Parkinson's disease is rare and is by no means so common as the other incomplete type, namely, paralysis agitans

without tremor. The diagnosis was based on the paralysis agitans type of the tremor: its occurrence during rest, diminution, or cessation during an active movement, and the synchronous vibratory character of the tremor, which had the same rhythm in all the extremities. It could be inhibited by the will, but reappeared in other parts of the body during the act of inhibition. Other additional signs indicating Parkinson's disease were: the infrequent winking, the posture of the hands, the expression of the face, the absence of associated movements of the arms in walking. It was thought that an *essential tremor* could be excluded because of the absence of any familial history, the unilateral onset in the right upper extremity, the gradual progression, and the Parkinsonian characteristics of the movements. The *chronic progressive cerebellar tremor* (dysynergia cerebellaris progressiva) [35] was also excluded because of the absence of an increase of the tremor on intention, as well as the absence of other cerebellar elements such as dysmetria, dysynergia, intermittent asthenia and hypotonia, which are associated with this disease.

Case 4.—

Summary.—A man, aged 35, *with progressive rigidity and tremor of the left arm, beginning at the age of* 30. *There was the Parkinsonian mask, monotony of voice, and the tremor and posture of the arm and hand characteristic of paralysis agitans.*

History.—The patient was referred to me by Dr. William D. Robertson, of Mount Vernon, New York. He was aged 35, married, and the father of two healthy children. His wife had had no miscarriages. He was a slate and tile roofer by occupation. There was no *family history* of any similar disease. His father died of apoplexy at the age of 79, and his mother was still living and in good health at the age of 65. He had one sister who died of pneumonia. There was a *previous history* of gonorrhœa twenty-three years ago which ran its course without complications. He denied ever having had lues. There was no history of any trauma. In childhood he had measles, chicken-pox and the mumps, and eleven years ago an attack of typhoid fever. He had, with these exceptions, enjoyed perfect health, and up to the onset of his present illness had been a robust and hard-working man.

The disease from which he now suffers began when he was aged 30, with a stiffness of the movements of the left hand. He stated that the hand and fingers tended to assume a flexion position, and indicated the posture which is so characteristic of paralysis agitans. For two years the weakness and stiffness of the left hand continued without intermission, gradually growing worse. Two years later a tremor of the left hand made its appearance, at first only when he was excited or angry. The tremor was regular and involved the wrist and fingers, later extending up the arm. There were at no time pains,

paræsthesiæ, heat or burning sensations, neither had he suffered from headache or vertigo. The right upper extremity and legs were subjectively not affected and his only complaint was weakness, stiffness, and tremor of the right upper extremity of insidious onset and gradual progression.

Physical examination.—He was a strong, well-developed man with dark hair, with none of the external evidences of premature senility. The face showed a slight but distinct Parkinsonian mask. The left hand, and in a lesser degree the right, tended to assume the flexion attitude of paralysis agitans (fig. 9).

FIG. 9. *Case* 4.—Paralysis agitans beginning at the age of 30.

The left upper extremity was the seat of a coarse, rhythmical tremor which varied from four to five vibrations a minute. This tremor diminished during an intention movement and could be partially inhibited by the will for a brief period of time. There were at times typical pill-rolling movements of the thumb and fingers. The right arm, legs and head were free from any tremor. The grip of the left hand was slightly weaker than that of the right. Dynamometer, right 50, left 40, and passive movements of the left upper extremity revealed a slight rigidity of the musculature, and the so-called cog-wheel symptom on making passive movements. The gait and station were normal, with the exception of the position of the left arm (and to a lesser extent the right), which was held in that stiff, motionless manner in walking which is so characteristic of paralysis agitans. There were none of the

associated movements of the upper extremities which usually accompany the act of walking.

The speech was low-pitched and slightly monotonous in tone and was evidently affected.

The pupils were equal and reacted promptly to light and accommodation. The sympathetic skin reflex was also present. There was no nystagmus. The tendon reflexes of both upper and lower extremities were present and of normal intensity. The abdominal and cremasteric reflexes were active and the plantar reflexes were of the flexor type. The muscle reflexes of the arms were normal on both sides. Vision was normal, and the ophthalmoscopic examination was negative.

The heart sounds were normal; the systolic blood pressure was 120, and the urine was negative.

This is an example, like Case 3, of paralysis agitans beginning in the early period of life. There was nothing in the appearance of the patient, or in the physical examination, to warrant the assumption of a premature senility. He was a perfectly healthy man for his age, save for the tremor and rigidity of the left arm, which, with the mask-like expression of the face and the low monotonous voice, were characteristic of paralysis agitans.

It is of interest to note that the awkwardness, stiffness and typical posture of the left hand (i.e., the rigidity) antedated the onset of tremor by two years.

Chapter III.—The Juvenile Type of Paralysis Agitans.

The occurrence of paralysis agitans in the earlier decades of life has been recognized for many years and has given rise to considerable discussion from time to time. This juvenile group has always been a rather disturbing element in an affection which otherwise has usually been regarded as a manifestation of premature senility. For it has been rather difficult to harmonize the theory of premature senescence with its occurrence in the two extremes of life. The consensus of opinion among those who have observed these cases has been that the juvenile and presenile types present no essential difference in their symptomatology, but not a few observers, on purely theoretical grounds, have doubted the identity of the underlying pathological lesions in these two groups of cases. So far as I am aware there has been no previous record of any pathological investigation by modern methods of the juvenile type of the disease.

Willige [76], in 1910, subjected to a rigid analysis all previously recorded cases of juvenile paralysis agitans and concluded that only twelve, or possibly fourteen of these, were typical examples of this malady. Of this number, six were of the familial type, and for this group he proposed the term "paralysis agitans juvenilis familiaris." In their other features, the juvenile group, except for the age and the rather high proportion of the "family type," showed the usual characteristics of Parkinson's disease, viz.: Progressive rigidity, the characteristic tremor, which however is often quite extensive and severe; the typical involvement of the face, posture, gait and articulation, and in a few instances subjective sensation of heat and a tendency to hyperidrosis.

Oppenheim [64], in a recent discussion of this subject, states that he has had occasion to observe several of these juvenile cases, and at one time inclined to the belief that they represented a separate clinical type. Later experience, however, did not confirm this point of view and he now regards the presenile and juvenile types of Parkinson's disease as essentially the same.

One very striking feature of the juvenile cases is the unusual frequency of familial incidence, in which two or more cases of the disease appear in children of a single family. This tendency I have regarded as favouring the theory of a system disease, which is my interpretation of the pathological changes found in Case 1 (see Chapter IV). Family types of this disease have been described by Siehr [70] (two cases), Bonhoeffer [50] (two cases), Bury [51] (two cases), Clerici and Medea [54] (four cases).

A review of these juvenile forms shows that there are certain points of difference which distinguish them from the presenile type. These are: the early age of onset, the more rapid progression of symptoms, the comparatively early involvement of the bulbar muscles, the rarity, or perhaps absence of the rigid form without tremor (paralysis agitans sine tremore) and the infrequency of subjective sensory symptoms.

In regard to the "rigid type" without temor, I would say that only one case, so far as I am aware, has run any part of its course without marked tremor, and that is the classical observation recorded by Charcot [53], and even here a slight tremor developed at a later period of the disease. This case was further distinguished by an atypical contractural condition of the extensor type.

A hemiplegic distribution was noted in the oft-quoted observation of Duchenne [56] and again in a more recent observation of Pelissier and Borel [65]. In both of these cases, however, the attitude and facial

expression were characteristic of Parkinson's disease, so that the disease was not strictly one-sided, but merely manifested a unilateral predominance, which is not uncommon in other system diseases of the central nervous system.

In practically all of the cases the tremor has been generalized, coarse and rhythmical. Involvement of the eyelids, face and tongue have also been of frequent occurrence. In the early stage especially, the marked tremor has suggested the possibility of multiple sclerosis, especially when associated with exaggeration of the tendon reflexes, tremor oculi and pseudo-clonus. This was so in my Case 1, which Sachs [68] regarded as closely related to multiple sclerosis, and it is quite possible that the cases of Jolly [59] and Krause [60] were of a similar nature. Case 3 of my series, when first observed, was an example of the paralysis agitans without rigidity.

The disease certainly presents a close similarity in some of its early features to multiple sclerosis and in certain of my cases the tremor oculi, speech disturbance, pseudo-clonus and pseudo-Babinski reflex awakened the suspicion of this disease, either alone or in combination, but the subsequent clinical course and the autopsy findings excluded definitely any such conjectures.

The occurrence in the juvenile period of multiple sclerosis and paralysis agitans in combination, or of a "paralysis agitans type" of multiple sclerosis, I would therefore view with considerable scepticism, until there is produced some more definite pathological evidence to the contrary. It is, however, well to emphasize the fact that the juvenile paralysis agitans, in the early stage, may simulate very closely disseminated sclerosis by reason of an excessive action tremor, speech disturbance, tremor oculi, pseudo-clonus and a spurious Babinski reflex.

Another interesting question is that of progressive lenticular degeneration. In this disease the average duration of the affection in the chronic form was four years; in the Homén [101] case as long as seven years was noted. Of late, there has been a tendency to classify cases of still longer duration as probable examples of Wilson's disease, notably in the case recorded by Sawyer [104]. In the more chronic forms of Wilson's disease, it would therefore be well to bear in mind progressive atrophy of the globus pallidus, as there are many points in common between it and progressive lenticular degeneration.

Chapter IV.—Pathological Findings in Juvenile Paralysis Agitans.[1]

Since the days of Parkinson, the pathology of paralysis agitans has been a fascinating field for speculation and study. Every method of histological research has at one time or another been brought to bear upon this important question, with variable and uncertain results. One great disadvantage, encountered by previous observers, has been the advanced age of the subjects upon which pathological studies have been made, so that senile degenerations, vascular and perivascular lesions have dominated or obscured the histological picture.

The case which is the subject of this study, because of the early age of onset (fifteenth year) and the comparatively early age of death (fortieth year), was free from this disadvantage, and the pathological findings were not obscured by widespread senile changes.

Report of Autopsy and Pathological Findings in Case 1.

Clinical diagnosis: Juvenile paralysis agitans. (For clinical description of case, see Chapter II.)

An autopsy was performed on January 29, 1914, twenty hours after death, by Dr. David Felberbaum, pathologist to the Montefiore Home. The body had been preserved on ice.

Autopsy Notes.

The body is moderately emaciated, with small decubiti over the buttocks, right shoulder and both heels. On opening the thoracic and abdominal cavities, the pericardial sac is found dry and free from adhesions. The heart muscle is flabby and of a brownish colour. The valves are normal. The aorta, including the arch, the thoracic and abdominal portions, show only a very slight development of atheromatous patches.

The lungs are free from adhesions and both present evidences of œdema. In the right lung, posteriorly and near the base, is a small calcified tubercle.

The liver is somewhat diminished in size and congested, presenting a distinct nutmeg appearance. There are no surface nodulations, nor evidences of cirrhotic changes on the surface of section.

The spleen is extremely small, measuring 3½ in. by 2 in. Its

[1] Demonstration of histological specimens to the New York Society of Internal Medicine, April 26, 1916.

consistency is increased and the trabeculæ are thickened and increased in number.

The kidneys are both of normal size, somewhat congested, and present the normal markings of cortical and medullary structure. The capsule strips readily, and there are no evidences of cirrhotic changes.

The adrenals are normal.

The thyroid gland is of normal size and appearance. In the left lobe, posteriorly, there is a small cyst about the size of a pea which contains a dark fluid.

The pancreas is normal.

The gastro-intestinal tract and the genito-urinary tracts show no abnormal changes.

The pituitary gland is of normal size and appearance.

Brain and spinal cord.—The calcarium is of normal thickness and the surface of the underlying dura is normal. The cranial cavity contains a moderate quantity of cerebrospinal fluid, the dura mater is not adherent and is of normal appearance. The leptomeninges are not thickened and there are no evidences of meningeal exudate or hæmorrhage. The cerebrum, cerebellum, and the brain-stem are normal to the naked eye. The vessels of the circle of Willis are soft and normal in appearance and show no evidence of atheroma or thrombosis. The cranial nerves are normal in size and structure, and the spinal cord is normal to the naked eye.

The brain, spinal cord and portions of the viscera were preserved in 10 per cent. formalin solution for histological study. After fixation, the corpus callosum was incised, revealing the mesial surface of the cortex and the interior of the lateral ventricles; no abnormality was discovered. A transverse section through the hemisphere was then made above the level of the corpus callosum (Marie's coupe d'élection) exposing the optic thalamus, lenticular nucleus, caudate nucleus and the internal capsule. The markings of this region were all perfectly normal and there was no evidence of any gross lesion, e.g., hæmorrhage, softening, or degeneration (fig. 10).

Microscopic Examination of the Viscera and Glands. (Dr. B. S. Kline.)

Myocardium.—The muscle cells are of good size and close to one another. With the high power these show marked blurring of the striations, the cytoplasm taking an almost homogeneous pink stain. The nuclei stain well and there is extremely little brown pigment around them. The striking alteration is the moderate diffuse increase in the interstitial connective tissue. The blood-vessels show considerable

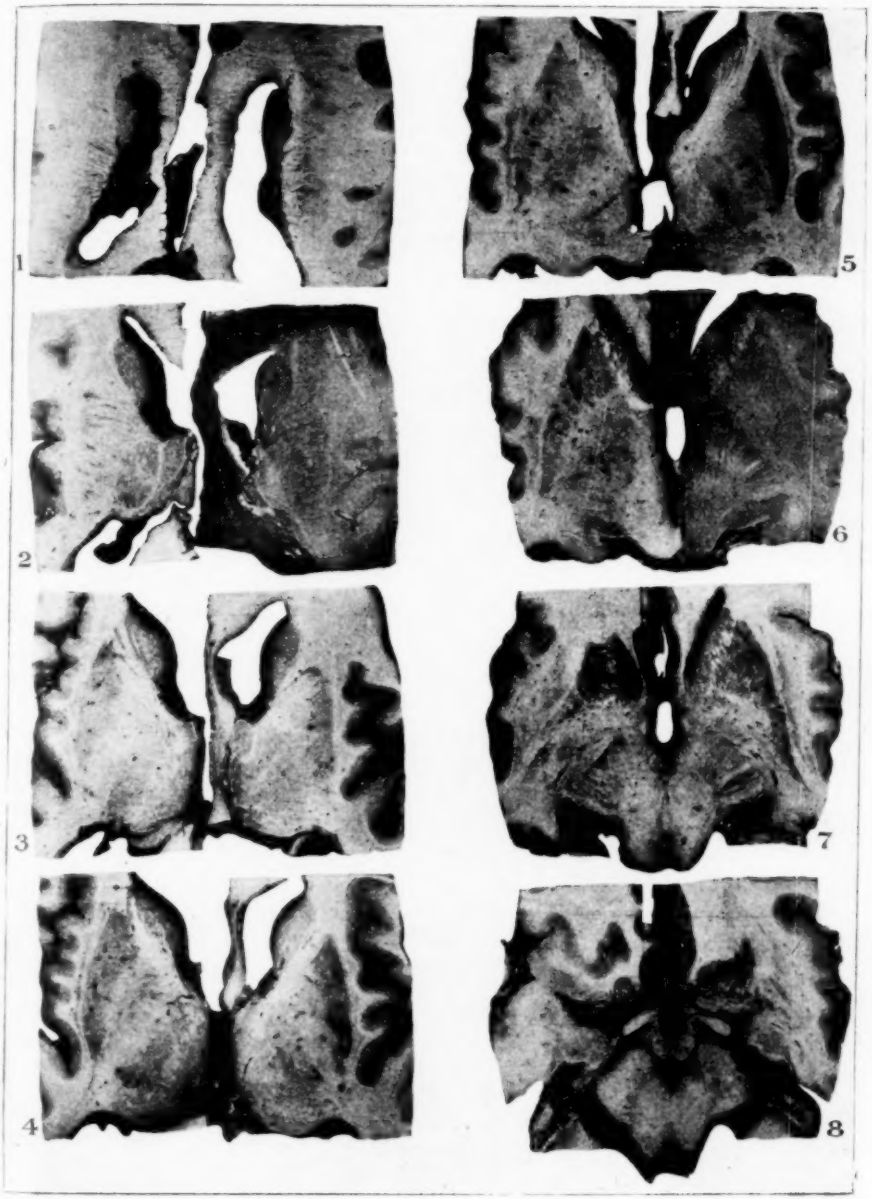

FIG. 10.—Horizontal sections after fixation, showing the gross appearance of the basal ganglia.

thickening of the intima. There are no definite areas of replacement fibrosis. About the blood-vessels there are grouped a number of fat cells.

Liver.—The lobulation is quite regular and the lobules are of good size. The capillaries, particularly near the centre, are slightly engorged. The liver cells are of good size, finely granular, with extremely few fat vacuoles anywhere in the section. There is a slight but definite increase in the connective tissue about the peripheral vessels of each lobule, with which there is associated in places a number of mononuclear wandering cells. There are rather numerous polymorphonuclear leucocytes in the capillaries.

Thyroid.—There is a striking increase in the interstitial connective tissue, in places associated with a few round cells. The blood-vessels show moderate thickening of the walls. The acini vary greatly in size; in general they are much smaller than normal; in places they are completely collapsed. Many are filled with a pink-staining amorphous material.

Spleen.—The striking thing is the apparent increase in the number and thickness of the trabeculæ. The capsule is also considerably thickened. There is apparent diminution of the pulp and the Malpighian bodies are small. The blood-vessels show moderate thickening. The pulp contains numerous nucleated cells. The sinuses are not appreciably thickened.

Pancreas.—The lobules are of good size, and in many places widely separated from each other by fat, a part of which shows definite necrosis, the cells being filled with a homogeneous pink staining material. Within the lobules are seen fairly numerous normal and altered fat cell accumulations. The islands of Langerhans are increased in number and size. The remainder of the parenchyma shows but little change. In places, however, there are definite signs of atrophy of the acini. This is true at the periphery of the lobules and also within them in the neighbourhood of the interstitial connective tissue, which is increased considerably in amount in many places. The vessels are moderately thickened.

Kidney.—The renal architecture shows a fairly regular arrangement. The capsule is thickened. There are numerous small scars extending a short way into the cortex, and a few small cysts. There is, in addition, a slight diffuse increase in the interstitial connective tissue. The blood-vessels are moderately thickened, the capillaries moderately engorged, and the tubular parenchyma moderately swollen. The lumina

are filled with homogeneous pink-staining material which in part is, apparently, cellular debris.

Adrenal.—The capsule is thickened: the zona glomerulosa not so well defined as normally, and the trabeculæ are prominent. The parenchyma shows no definite abnormality.

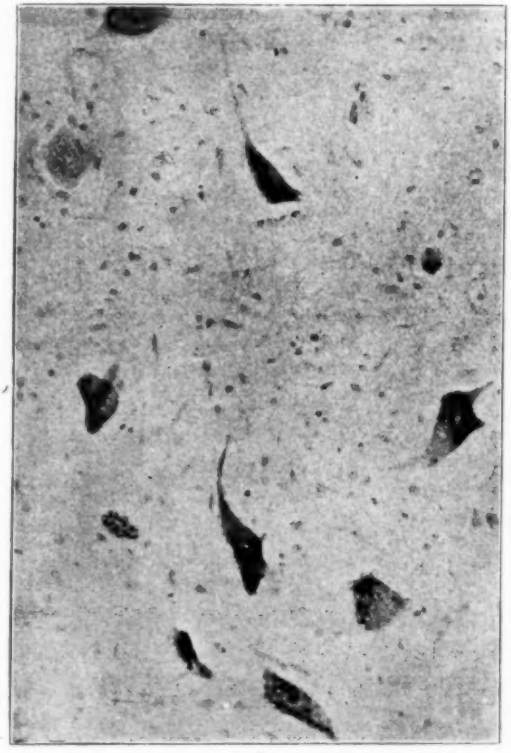

FIG. 11.—Toluidin blue. × 1,376. Normal cells of the anterior horn; lumbar region.

Microscopic Examination of the Central Nervous System.[1]

In the study of the various regions of the brain and spinal cord, the following stains and histological methods are employed, viz.: the

[1] The sections of the central nervous system were prepared in the New York Psychiatric Institute, under the direction of Dr. Charles B. Dunlap.

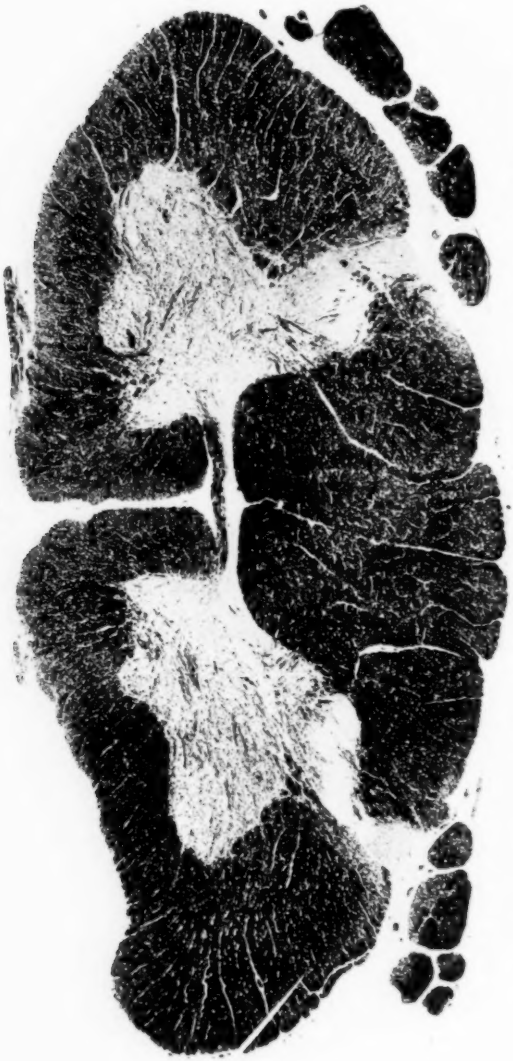

FIG. 12.—Weigert-Pal: spinal cord, cervical region. Note the absence of ascending or descending degenerations.

Weigert-Pal, Kulschitsky, hæmatoxylin-eosin, van Geison, Sim's hæmatoxylin, the Weigert and Cajal glia stains and toluidin blue.

Spinal cord.—Sections were prepared from the cervical, dorsal and lumbar regions of the cord. The ganglion cells were of normal appearance and staining reactions at all the levels examined. The large motor cells of the anterior horns are well preserved, both in number and configuration; the nuclei are normal in appearance and situation, and the Nissl bodies are sharply defined and of normal tigroid appearance (fig. 11). There is no excess of pigment in the anterior horn cells, and the moderate amount of pigment which is present is of a light yellow colour. There is no increase of the glia cells, nor of the connective tissue; the blood-vessels show in certain areas a moderate thickening of the media. There is no evidence of vascular occlusion or thrombosis, and no inflammatory foci or areas of round-cell infiltration are present in the neighbourhood of the blood-vessels. There is no perivascular gliosis or sclerosis, and the spinal meninges are normal. A study of the Weigert-Pal sections reveals no evidence of any tract degenerations and the anterior and posterior roots are both normal. The pyramidal tracts are free from any evidences of atrophy or degeneration (fig. 12).

Medulla oblongata and pons.—The Weigert-Pal method reveals no evidence of atrophy or degeneration of the medullated nerve-fibres in any of the fibre systems of the medulla or pons (fig. 13). The pyramids present a normal appearance, and there is no loss of fibres or increase of the glia constituents. The olives and accessory olivary nuclei, the restiform bodies and the fillet are normal. The cells of the nucleus ambiguous and of the hypoglossal nucleus stained with toluidin blue are well preserved and of normal appearance. They contain no excess of pigment. The dorsal vagus nucleus is also well preserved; its various cell groups are distinguishable and their number is not diminished. Many of these cells are, however, deeply pigmented, and some are completely infiltrated with dark brown pigment granules. This portion of the brain-stem is quite free from vascular lesions or inflammatory foci.

Cerebellum.—The ganglion cells of the cerebellar cortex and of the dentate nuclei are perfectly normal in appearance and there is no diminution in their number (fig. 14). There are no inflammatory foci or vascular lesions. The fibre systems of the cerebellar peduncles are free from any evidences of atrophy or degeneration.

Crus.—There are no evidences in the Weigert-Pal specimens of degeneration of the pyramidal tracts or of the fibre systems of the

FIG. 13.—Weigert-Pal; the pons varolii.

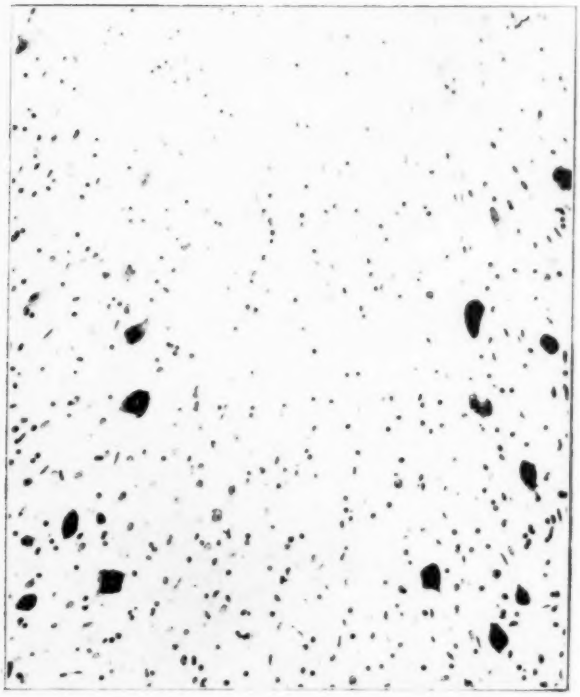

FIG. 14.—Toluidin blue. × 1,376. Showing cells of the dentate nucleus.

tegmentum. The medullary capsule and intranuclear network of the red nucleus are apparently normal, and the nucleus itself is of good size. The cells of the nucleus ruber are not diminished in number and are free from degenerative changes (fig. 15). The cells of the substantia nigra are also normal in number and appearance.

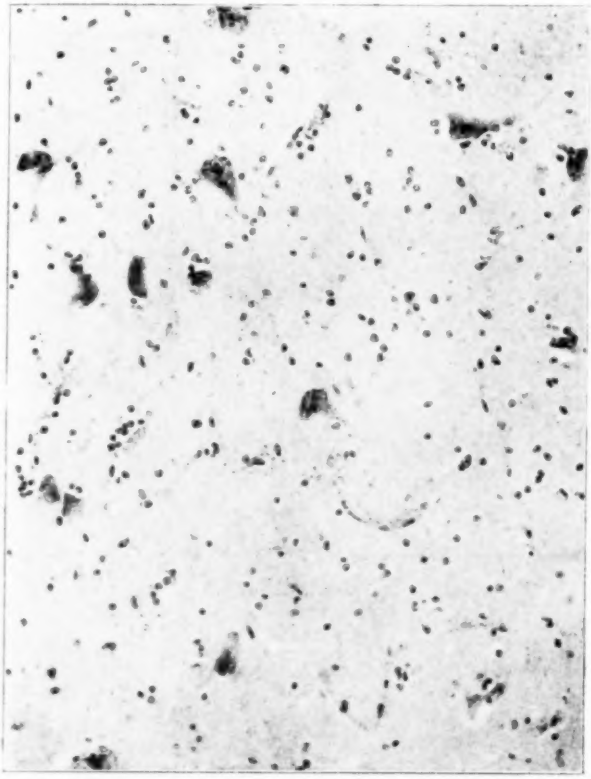

FIG. 15.—Toluidin blue. × 1,820. Showing normal cells of the nucleus ruber.

Basal ganglia, internal capsule and hypothalamic region.—As the macroscopic appearance of the surface of section through the basal ganglia was normal and quite free from gross evidences of degeneration, discoloration or softening, it was thought best to utilize the tissue of this region in such a way that specimens could be prepared

for tract studies by the Weigert-Pal method as well as for finer histological studies by purely cellular methods. The region of the basal ganglia was therefore removed as a single block of tissue and sectioned horizontally in serial slices approximately 3 mm. thick. The topmost slice included the under-surface of the corpus callosum, and the lowest slice passed through the corpora mammillaria. These were numbered from 1 to 8 and photographed (see fig. 10). The cut surfaces showed no gross focal lesions, but the blood-vessels were injected and stood out sharply from the rest of the tissue; especially is this true of No. 7, which passes through the optic tracts just above the level of the anterior perforated space. From these a series of sections at various levels was stained by the Weigert-Pal method, and sections from other blocks were prepared for finer histological study, and stained with toluidin blue, hæmatoxylin-eosin, Van Gieson and Sim's hæmatoxylin. The sections for cellular and finer histological study were cut in paraffin, and were from 8 to 10 microns in thickness. Sections were also stained for glia by the Weigert and Cajal methods.

The Finer Histological Structure of the Basal Ganglia.

Lenticular nucleus.—The blood-vessels of this region, especially in the more basal sections, show some thickening of the media and adventitia, and in certain areas a well-marked enlargement of the perivascular spaces. There is, however, no endarteritis, and no evidences of thrombosis in any of the sections. In certain perivascular spaces of the globus pallidus, and more especially of its inner segment, a moderate accumulation of yellowish pigment and granular detritus is to be found. This is, however, a rare finding, and when present was not excessive. The sections are quite free from round-cell infiltration and inflammatory foci.

Globus pallidus.—In the globus pallidus, and more especially in its inner segment, near the angle formed by the bend of the internal capsule, there are numerous, highly refractive, concentric or irregularly elongated bodies, which take an intensely blue stain with hæmatoxylin. Some of these bodies are pear-shaped and others tubular. Not infrequently in the immediate region numerous smaller translucent circular bodies are evident, not much larger than a leucocyte and resembling corpora amylacea. These have somewhat the appearance of calcareous deposits (corpora arenacea), and were not present to the same degree in the putamen, the caudate nucleus, or in the peripheral region of the globus pallidus.

On examining sections of the globus pallidus stained by the Nissl method, a reduction in number and diminution in size of the ganglion cells of this region is quite evident (figs. 16 and 17). Instead of the usual groupings of rather large motor cells with the tigroid arrange-

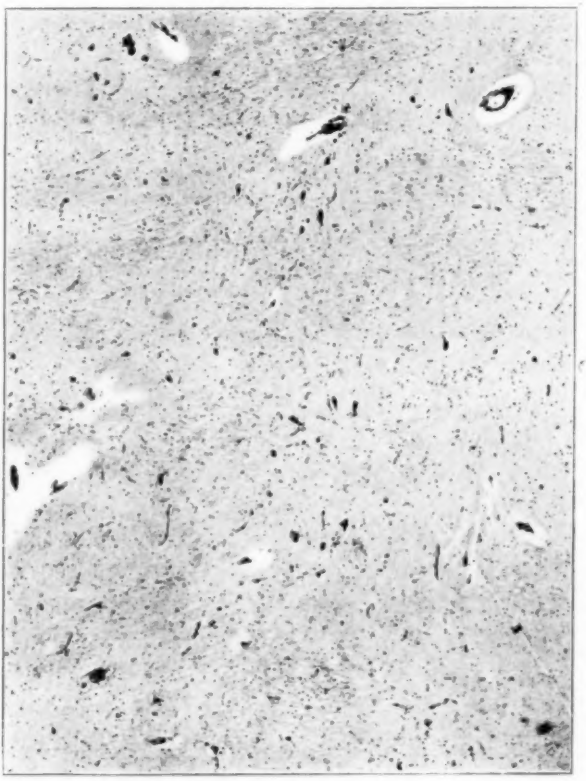

FIG. 16.—The globus pallidus; external segment; toluidin blue. × 384. Showing general atrophy and diminution in number of the large motor cells of the globus pallidus system. Note the moderate increase of glia nuclei and the large hyalin concrements staining intensely blue.

ment of granules, there are sparsely distributed cells, many of which are in various stages of chronic atrophy (figs. 19 and 20).

The cell body is frequently atrophic or shrunken, and the cell processes fragmented, rounded, or presenting a twisted, corkscrew

appearance. Some of the atrophied cells are uniformly hyalin and highly refractive. There are also empty spaces in the midst of atrophic cells from which the diseased cell had probably been removed. In many of the cells the nucleus cannot be differentiated, as the entire cell takes on a diffuse stain. When the nucleus is visible it is often diffusely stained, shrunken or elongated, with roughened contour or displaced from the centre of the cell. Some of the atrophic cells are surrounded

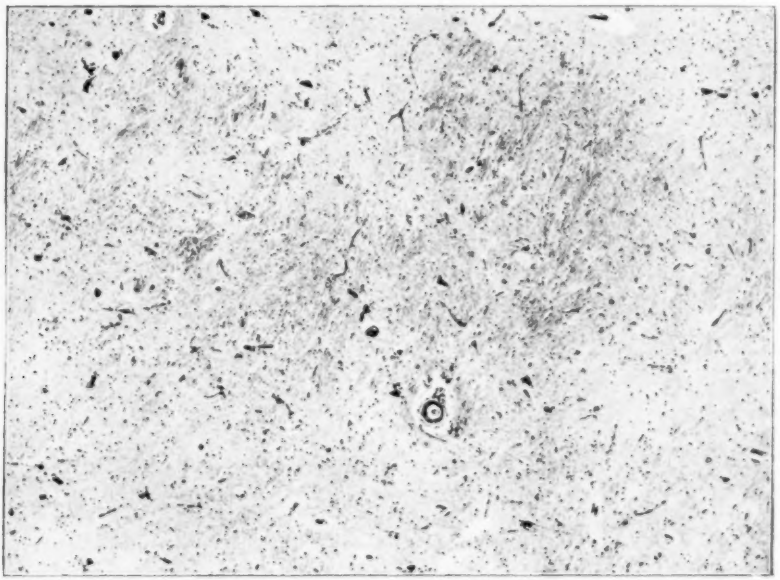

FIG. 17.—Globus pallidus; internal segment; toluidin blue. × 384. Showing atrophic cells of the globus pallidus; numerous rounded and irregularly-formed concrements and moderate increase of glia nuclei.

by groups of parasite glia cells; occasionally these are contained within the substance of the cell (neuronophagia).

Here and there, especially in the more peripheral portion of the globus pallidus near the putamen, small groups of comparatively normal looking cells are observed, with sharply defined contour and processes, a well-differentiated nucleus and nucleolus, and normal groupings of the Nissl granules. Such cells are in marked contrast to the large number of diseased cells showing various stages of chronic atrophy.

The cells and cell remnants of the globus pallidus are singularly free from evidences of fatty or pigmentary degeneration; indeed, the pigment deposit is, if anything, less than that which is usually met with in this region.

Nucleus basalis.—In the infralenticular region beneath the globus pallidus the cells of the nucleus basalis of Meynert also appear diminished in number and some show evidences of chronic atrophy. In this

FIG. 18.—Section of normal globus pallidus; toluidin blue. × 1,820. For comparison.

nucleus, however, a number of normal-looking cells of the globus pallidus type are still present, and the evidences of cellular wasting in this structure are not so advanced as in the globus pallidus proper, although atrophic changes are undoubtedly present.

Under normal conditions the ganglion cells of the globus pallidus type, both singly and in groups, are to be found scattered among the fibres and the radiations of the ansa lenticularis as they traverse the internal capsule. In my sections, these cells are not only diminished in number, but when present show atrophic changes.

There are no evidences of acute cellular degeneration, e.g., powdered appearance of the granules, swelling of the cell body and dislocation of the nucleus. The cellular changes are purely those of chronic atrophy without pigmentation or acute degeneration. There are no fat granule cells.

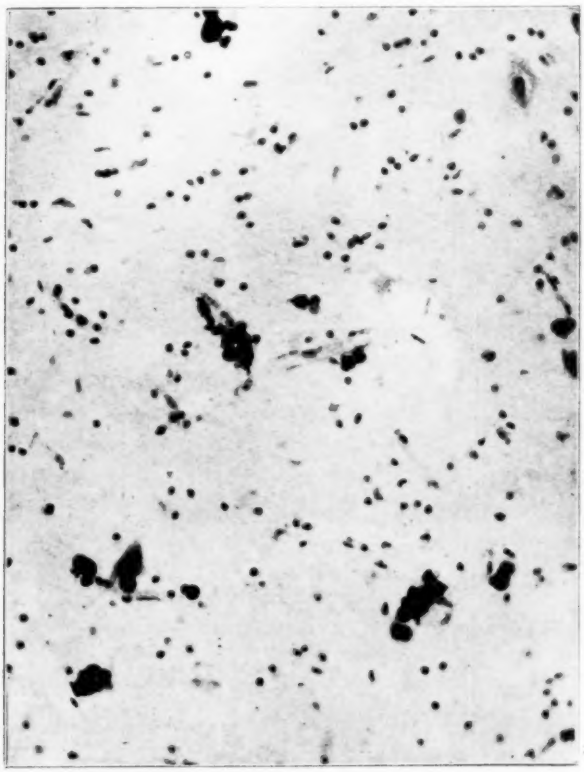

FIG. 19.—Atrophy of the globus pallidus; toluidin blue. × 1,820. Showing atrophic cells; increase of glia nuclei and irregular hyaline concrements.

The *glia cells* of the globus pallidus are increased in number. This increase is distributed rather generally throughout this structure and is nowhere massive nor in large clumps; not infrequently a group of three or four glia cells is found in the pericellular space of an atrophied cell, and small isolated groups of from five to ten cells are not uncommon. There is no especial proliferation of the glia fibres in specimens stained

by the Weigert method. Cajal's glia stain shows a number of spider cells, fairly evenly distributed throughout the globus pallidus.

Putamen.—The small polygonal and stellate ganglion cells of the putamen, which constitute the chief cellular content of this region, are not diminished in number and show no evidence of atrophy. On the other hand, the large multipolar cells of the globus pallidus type which are normally scattered throughout the putamen, show very marked

FIG. 20.—× 3,320. Toluidin blue ; showing atrophic cells of the globus pallidus system.

changes. These large cells of the putamen are greatly diminished in number and the few which are still preserved show evidences of atrophy (fig. 21). It is rather difficult to find any of these large ganglion cells in this region, as their loss is so considerable, and when present they show marked evidences of chronic atrophy. The atrophy and disappearance of these larger cells of the putamen were noted at all the levels examined and were very evident in sections from the upper level of the lenticular region before the appearance of the globus pallidus.

There is also a general increase of the glia nuclei in this region; small aggregations of from six to ten glia nuclei are not uncommon. The Cajal method shows the presence of occasional spider cells. The increase of glia cells, together with the large number of small ganglion

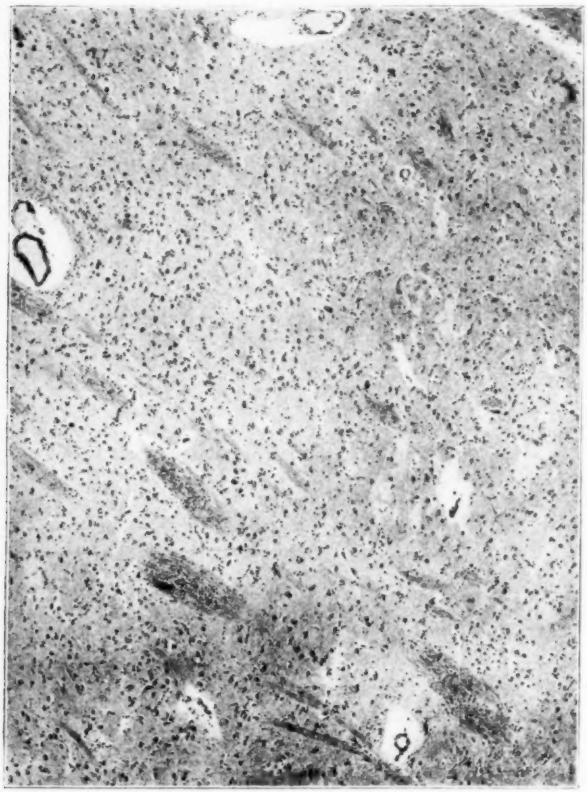

FIG. 21.—Progressive atrophy of the globus pallidus; section through the putamen; toluidin blue. × 384. Note the increase of glia nuclei and almost complete absence of the large globus pallidus cells. The small ganglion cells are not reduced in number.

cells which is peculiar to this region, give to the putamen a very cellular appearance, in spite of the loss of the larger ganglion cells of the globus pallidus type (fig. 22).

Caudate nucleus.—Cellular changes, similar to those found in the

putamen, are also present in the caudate nucleus. The large ganglion cells of the globus pallidus type are in this region also considerably diminished in number, and those remaining show various stages of chronic atrophy (figs. 23 and 24). They were shrunken and atrophic,

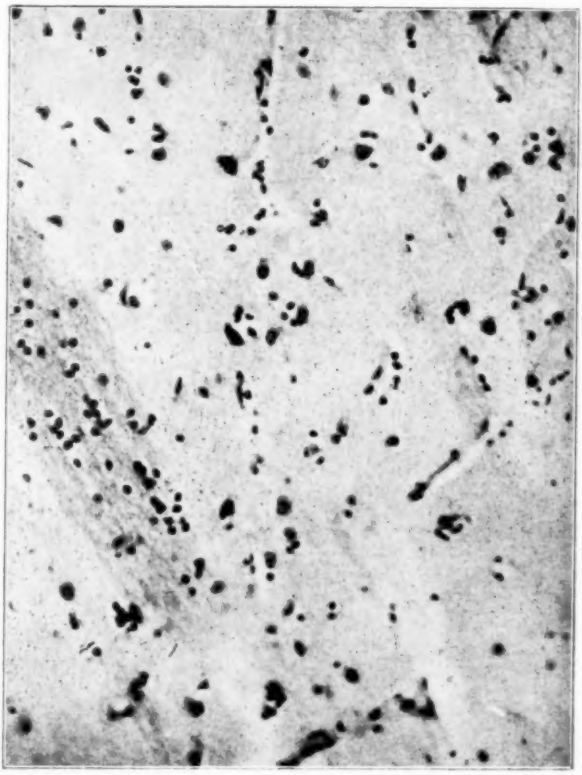

FIG. 22.—Putamen; toluidin blue. × 1,820. Showing increase of glia nuclei and absence of large globus pallidus cells.

often opaque, the entire cell staining intensely blue with hæmatoxylin, without differentiation of the various constituents of the cell. In other cells, the nucleus was diffusely stained and the cell processes shrunken or broken off. The numerous, small, polygonal ganglion cells which normally predominate in this region were undiminished in number and

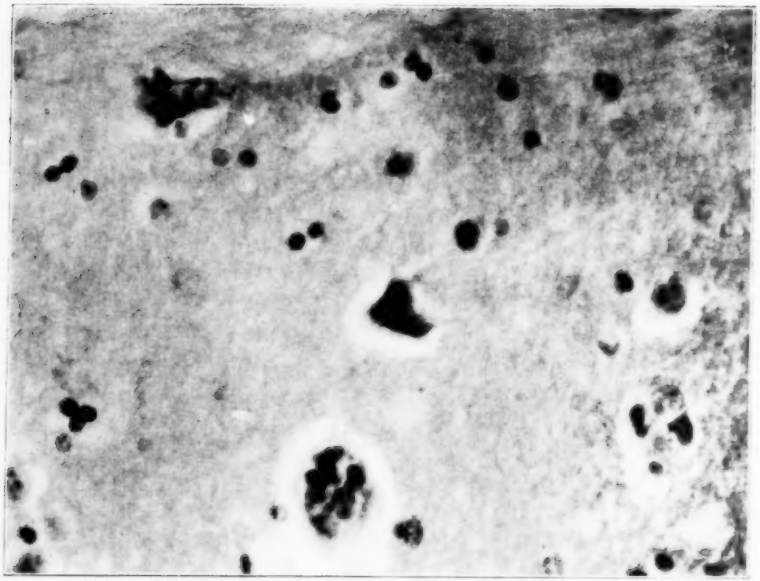

FIG. 23.—Caudate nucleus; toluidin blue. × 3,840. Showing atrophy of a large multipolar cell of the globus pallidus system.

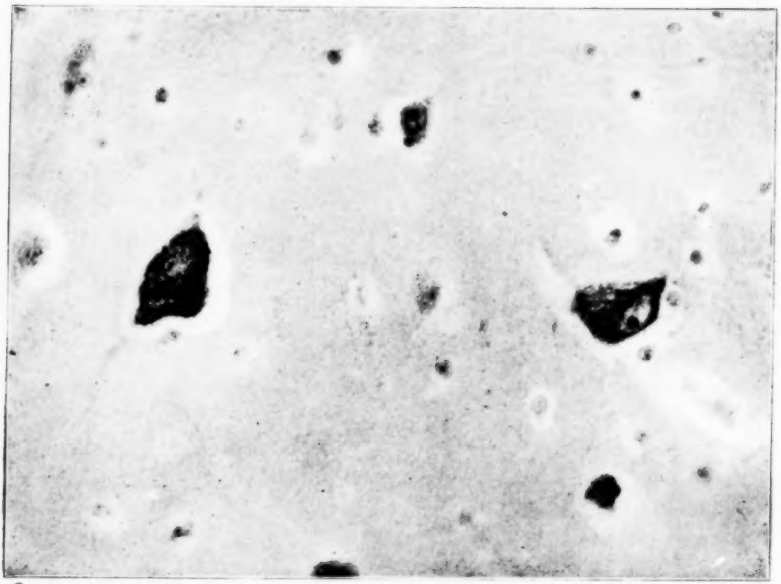

FIG. 24.—Section of normal caudate nucleus; toluidin blue. × 3,840. For comparison, showing large motor cells of the globus pallidus system.

were not atrophied. There was also a moderate increase of the glia nuclei, but less than was noted in the putamen.

Comparative cell counts of the corpus striatum.—While the diminution in number of the large cells of the globus pallidus, putamen and caudate nucleus was quite evident in the various sections examined, in order to obtain a more exact idea of the degree of cell loss a number of comparative cell counts were made. The control specimens utilized for this purpose were obtained from the brain of a young adult who had been electrocuted and whose brain had been removed immediately after death and preserved in formalin, so that the control tissue was in all respects normal. Sections were cut at the same levels as were those of the case of juvenile paralysis agitans, and were stained by the same histological methods. The cell counts were made with both the high and low power of the microscope, and a considerable reduction of the number of globus pallidus cells was constantly present in all of the pathological specimens. The degree of cell loss varied somewhat in the different regions of the corpus striatum. In the globus pallidus the average reduction varied from one-sixth to one-quarter; in the putamen one-half to three-quarters; and in the caudate nucleus about one-half to two-thirds as compared with the cell counts of normal specimens.

There was, therefore, a considerable reduction in the number of the large ganglion cells of the corpus striatum (globus pallidus type) in all its segments, viz., the globus pallidus, the putamen, and the caudate nucleus. The diminution in the number of cells of the globus pallidus type was very striking, both in the neostriatum (caudate and putamen) and in the paleostriatum (globus pallidus), and was especially marked in the putamen.

I would again emphasize the fact that those cells which persisted were by no means normal in appearance, but were in various stages of chronic cellular atrophy. Normal cells of the globus pallidus type were occasionally met with. They were, however, few in number, and served by contrast to emphasize the chronic atrophic changes in the neighbouring cells. Their presence would also tend to show that the fixation and staining of the tissue in this region was satisfactory.

Optic thalamus.—The cell groupings of the optic thalami, the nucleus anterius, nucleus externus, nucleus medialis, nucleus internus and the pulvinar, are well preserved and apparently normal. There are no evidences of cell loss or atrophy and no increase of glia nuclei. The blood-vessels are free from thrombosis or endarteritis, and no inflam-

matory foci are noted; as in the lenticular region and elsewhere throughout the brain, some thickening of the media and adventitia is present, but the lumen of the vessel was nowhere occluded.

Corpus subthalamicum.—The ganglion cells of the corpus Luysii are of normal appearance and are not diminished in number (fig. 25).

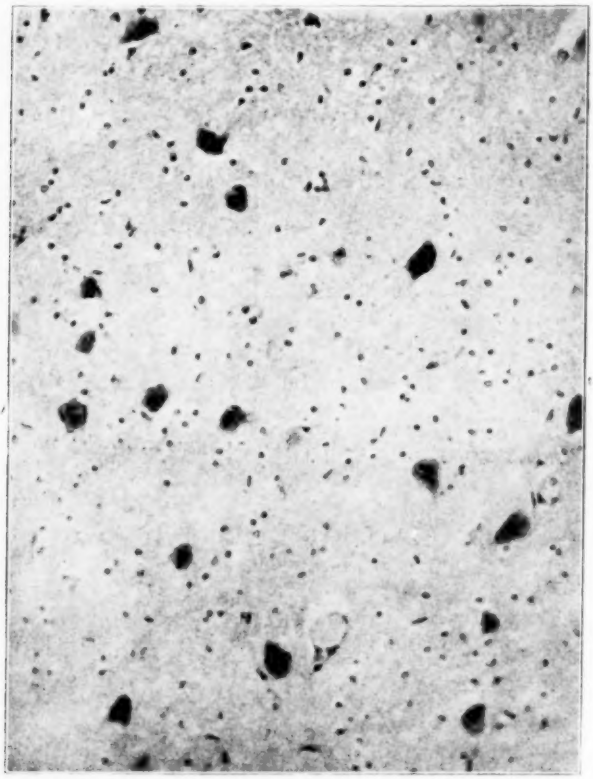

FIG. 25.—Toluidin blue. × 1,820. Showing normal cells of the corpus Luysii.

Nucleus ruber.—The cells of the red nucleus, both the smaller and larger types of ganglion cells, are of normal appearance and undiminished in number.

Cortex cerebri.—Blocks of tissue were removed from the right and left frontal region, the anterior and posterior Rolandic areas on both

sides, the right and left gyri recti, as well as the angular gyrus, the occipital and the temporal convolutions. These were stained with toluidin blue, hæmatoxylin-eosin, Van Gieson, Sim's hæmatoxylin and by the Weigert-Pal methods. No noteworthy pathological changes were found in the cerebral cortex.

The meninges are normal and the blood-vessels, save for a moderate degree of arteriosclerosis, present no abnormalities. There are no endarteritis, no round-cell infiltration, and no areas of degeneration, hæmorrhage or necrosis.

FIG. 26.—Weigert-Pal method. Horizontal section through the corpus callosum and upper level of the basal ganglia; showing the thalamus, nucleus anterius, caudate nucleus and internal capsule.

The cyto-architectural appearance of the cortical layers is well preserved and there is no evidence of cellular atrophy or degeneration. Occasionally, isolated, atrophic cells are observed in the deeper pyramidal layers of the cortex, but these are exceptional and infrequent. There is no excess of pigment deposit in the cells of the cortex.

Of special importance is the state of preservation of the Betz cells in the precentral gyrus. These show no reduction in number, they are of normal size and appearance, and contain no excess of pigment.

In sections of the cerebral cortex stained by the Weigert-Pal method, the tangential layer of fine fibres and the cortical radiations show no material change or diminution.

FIG. 27.—Weigert-Pal method. Horizontal section through the optic thalamus, internal capsule and corpus striatum. (Pale area in posterior limb of internal capsule due to defective stain.)

The tracts and fibre systems of the basal ganglia.—Serial sections were prepared from various levels of the basal ganglia and stained by the method of Weigert-Pal (see figs. 26, 27, 28, 29 and 30).

In these sections there are no evidences of sclerosis, cavity formation, or other gross destructive lesion of the basal ganglia. Furthermore, the various constituents of the corpus striatum, viz., the caudate nucleus, the putamen and globus pallidus, are normal in size and configuration.

The body of the putamen appeared as if slightly reduced in size. This was, however, slight and could not be determined with certainty. Both the anterior and posterior segments of the internal capsule are normal in appearance, as are also the retrolenticular segment and the fasciculus temporo-pontinus (Türck's bundle).

FIG. 28.—Weigert-Pal method. Horizontal section through the lenticular nucleus and subthalamic region; showing moderate thinning of the ansa lenticularis.

The fibre systems of the lenticular nucleus, viz., the radiating fibres and the outer and inner medullary layers, show the usual markings and distributions. Both the external and internal medullary laminæ of the globus pallidus are fairly well developed and their supplementary laminæ are also present, and while there seems to be a slight general reduction in the number of fibres in the globus pallidus, this could not be determined with certainty by this method. Such a diminution, if slight and evenly distributed, would be very difficult to determine in specimens stained by the Weigert method.

The small, pencil-like groupings of medullary fibres which traverse the caudate nucleus and the putamen, radiating towards and through the globus pallidus, are well developed, and show no diminution in size or number.

The external capsule, the claustrum and the various medullary layers of the optic thalamus are normal and well developed.

FIG. 29.—Weigert-Pal method. Horizontal section through the cerebral peduncle and basal portion of the corpus striatum ; showing thinning of the fibres of the ansa peduncularis.

Of especial interest and importance in a case of this character are the striothalamic and hypothalamic radiations. The striothalamic radiations are apparently undiminished in number and no distinct evidences of atrophy could be determined by this method. The hypothalamic radiations, on the other hand, present slight but definite signs of atrophy. There is a distinct thinning of the fibres and fasciculi of Forel's lenticular bundle (H_2), the strio-Luysian radiations and of the ansæ lenticularis

and peduncularis. The layer of fibres between the globus pallidus and the internal capsule (stratum capsulo-lenticulare) also shows a reduction in size. Many of the fibres of the ansal system, as they cross the posterior segment of the internal capsule and the crus cerebri, are thin and poorly developed, and while there is nowhere a total loss of the strio-hypothalamic radiations, a general thinning of the ansal system is quite evident.

FIG. 30.—Weigert-Pal method. Horizontal section through the crus cerebri.

The corpus Luysii is not materially reduced in size. Its ventral and dorsal capsule of medullated nerve fibres is less voluminous than usual, and the fibres of the intraganglionic network also appear somewhat reduced in number.

Forel's commissure which traverses the hypothalamic region between the two Luysian bodies is present, and so far as could be determined was not atrophic.

Evidences of Meynert's commissure are also present in my specimens, but whether the fibres of this commissure had suffered any diminution in number could not be determined with certainty.

The tegmental region, the capsule and medullary network of the nucleus ruber and Forel's thalamic bundle (H_1), are normal in size and appearance.

Other structures—e.g., the fasciculus longitudinalis posticus, the fillet, the fasciculus retroflexus of Meynert and of Vicq d'Ázyr—are normal.

Résumé of Pathological Findings.

A general autopsy was performed twenty hours after death and revealed no essential lesion of the thoracic or abdominal viscera. The liver structure was normal and quite free from cirrhotic changes. The thyroid, adrenals and hypophysis cerebri were normal.

The brain and spinal cord were normal to the naked eye; the meninges were not thickened and the vessels of Willis were smooth and practically free from arteriosclerotic changes.

A careful study of the central nervous system by modern histological methods showed no essential lesions, excepting of the corpus striatum. In this region, the cells of the globus pallidus type were diminished in number; the reduction estimated by comparative cell counts varied from one-sixth to one-half of the normal. The greater number of the remaining cells were in various stages of chronic atrophy. These cellular changes were not confined to the cells of the globus pallidus proper, but were also evident in the nucleus basalis of Meynert, which lies beneath the globus pallidus in the substantia innominata of Reichert. I would also particularly emphasize the fact that the large cells of similar type which are normally present among the small polygonal ganglion cells of the caudate nucleus and putamen were also considerably reduced in number and in various stages of chronic atrophy.

The cellular atrophy in this case was therefore confined to a single type of cell, viz., that of the globus pallidus. It was apparent in the globus pallidus proper, also in the nucleus basalis of Meynert and was especially marked in the caudate nucleus and putamen (the neostriatum). I therefore look upon the globus pallidus cells of the corpus striatum as a well-defined anatomical and physiological system, the *pallidal system* or the *globus pallidus mechanism*, and would regard this as the essential motor or projection system of the striate body.

There was a moderate increase of the glia cells of the globus pallidus, and also of the putamen and the caudate nucleus. There was however

no increase of the glia fibres. This I regard as a replacement manifestation, secondary to the atrophy of the motor neurones of the globus pallidus system. The blood-vessels of the corpus striatum showed in certain areas a moderate thickening, but no occlusions and no evidences of any serious vascular or perivascular disturbance. In the globus pallidus there were many calcareous bodies of concentric form which were especially numerous in its inner segment. These have no especial pathological significance, as they are found in every decade of life and as a complication of many diseases. (Wollenberg [47]).

Corresponding to the atrophy of the efferent cells of the globus pallidus mechanism, there was a moderate thinning of the striohypothalamic radiations, viz.: the lenticular bundle of Forel, the strio-Luysian fibres and the ansæ lenticularis and peduncularis. This diminution was moderate in degree, and was evenly distributed. It was nevertheless quite evident. The medullary network of the globus pallidus and of the corpus Luysii also seemed to have undergone some slight diminution, but this was difficult to determine by the Weigert method, and if present it was evenly distributed and moderate in degree.

The small commissures of Forel and of Meynert which traverse the floor of the third ventricle were both demonstrable. The striothalamic radiations, the medullary laminæ of the thalamus, Forel's thalamic bundle and the various nuclei of the optic thalamus showed no abnormalities.

The internal capsule and the pyramidal tracts were normal throughout. The cells of Betz of the Rolandic area and the anterior horn-cells were also normal in appearance and number. Indeed, a careful histological study of the various areas of the cerebral cortex, cerebellum, pons, medulla and spinal cord failed to reveal any evidences of pathological changes which might in any way be considered as the lesion of this disease.

The only discoverable lesion was a widespread atrophy and disappearance of the cells of the *globus pallidus mechanism*, viz., the globus pallidus proper, the nucleus basalis of Meynert and especially the large cells of the neostriatum. I therefore regard this affection as a progressive atrophy of the motor cells of the globus pallidus mechanism, and this mechanism as the essential motor or projection system of the corpus striatum.

Chapter V.—Progressive Atrophy of the Globus Pallidus.

On account of the obscurity surrounding the true nature of paralysis agitans, any classification of its various types has been a purely clinical one, the inevitable result of our meagre knowledge of its underlying cause and pathology.

We are in the same position toward this type of paralysis as would be the case with the spastic paralyses if the course and function of the pyramidal tracts were unknown.

An exact knowledge of the origin, course and termination of the pyramidal tracts has permitted not only clinical, but important pathological subdivision, the latter being the more important of the two for the purposes of classifying disease. If paralysis agitans could be subjected to a similar method of pathological differentiation it would simply be following a precedent which has been recognized in the classification of every organic affection.

With this end in view I would suggest a separation of the juvenile and early adult forms of paralysis agitans from the larger syndrome on the basis of the pathological alterations in the motor neurones of the globus pallidus system.

For this affection I would propose the name, *progressive atrophy of the globus pallidus*, as best expressing the nature, characteristics and localization of the abiotrophic process. The term "globus pallidus" as used here refers to the globus pallidus mechanism, and includes all the cells of the pallidal type in the corpus striatum, namely, those of the putamen, caudate, nucleus, and the globus pallidus proper. *Primary atrophy of the pallidal system* is equally descriptive, and may be found preferable as a designation for this type of atrophy.

Further pathological investigation will be necessary in order to show how frequently these same pathological changes are met with, when the disease begins in the later period of life. I suspect, however, that in the late forms of the disease, senile degenerations, vascular and perivascular lesions will play the more important rôle.

Definition.—The progressive atrophy of the globus pallidus may therefore be defined as a system disease which is clinically of the "paralysis agitans type," and pathologically is associated with atrophy of the motor cells of the globus pallidus mechanism. It is a pure system disease, an *abiotrophy*, in the sense in which this term was used by Gowers, and is characterized by a progressive degenerative atrophy limited to a definite system of neurones. In this respect it

resembles primary lateral sclerosis and the progressive muscular atrophy, and is another example of the vulnerability of the motor neurone. The affection is often familial and is sometimes hereditary (Gunther [81]). It appears in the second or third decade of life, and, like other system diseases, perhaps even later.

The *etiology* is unknown. It begins insidiously and progresses slowly and steadily, without apparent cause. Some cases have followed, or their course has been exaggerated by the acute infectious diseases. In Case 3 of my series syphilis had preceded the onset of the symptoms. Trauma has also been cited as an exciting cause. But here, as in the other forms of abiotrophy, we are in a mysterious field in which a primary biological weakness of the affected system of neurones or an occult form of selective intoxication probably plays the important rôle. In one of my cases there was consanguinity of the parents, which is so important a factor in the production of other forms of system disease.

The *symptomatology* is comparatively simple and is limited to a progressive paralysis, rigidity and tremor in various combinations. It begins with rhythmical tremor and rigidity of an extremity which then gradually extends to other portions of the body. The affection is usually bilateral, although there may be a unilateral predominance of the symptoms over a number of years. The paralysis, rigidity and tremor have all the characteristics of paralysis agitans. In the early stage the tremor is often coarse, and may become violent during emotion or motor activity. It is not of the intention type and gradually diminishes and finally ceases as the movement reaches its termination. In advanced cases, the face, tongue, eyelids and ocular excursions may be affected. The ocular tremor may then simulate closely a true nystagmus and a spurious ankle clonus may also be present.

As the disease advances the tremor usually recedes and the paralysis and rigidity become more prominent. The paralysis and rigidity are those characteristic of paralysis agitans. There is the rigid musculature, the mask-like expression of face, the slowness of movement, the lack of motor initiative and the typical gait and posture so well described by Parkinson. The paralysis, apart from the rigidity, involves essentially the automatic and associated movements. The affection is inclined to progress somewhat more rapidly than the late forms of paralysis agitans, and involvement of the bulbar muscles may occur comparatively early in the disease. In the last stage there is almost total rigidity of the entire voluntary muscular system.

There is no pathological exaggeration of the tendon or periosteal

reflexes; the abdominal reflexes are preserved until such time as the abdominal walls are so rigid that they are no longer able to respond to reflex stimulation, and the plantar reflex is of the flexor type.

Occasionally, a spurious Babinski sign is produced, apparently by rigidity of the extensor longus hallucis muscle. This disappears if the reflex is tested after the leg has been flexed at the knee. It is, therefore, a pure extra-pyramidal motor disturbance, and the corticospinal system is intact.

The special senses and general sensation are normal, and in uncomplicated cases the mind is unaffected. The clinical picture is limited to a paralysis of automatic and associated movements, hypertonicity and tremor.

Pathology.—The pathological lesion which underlies this malady is a progressive atrophy of the motor cells of the globus pallidus system. The cells of this system are found in the globus pallidus proper, the nucleus basalis of Meynert, and also in the caudate nucleus and putamen (neostriatum). This constitutes the globus pallidus mechanism and is the efferent motor system of the corpus striatum (pallidal system).

Corresponding to the cellular atrophy, there is also a thinning of the fibres of the hypothalamic radiations, viz., the lenticular bundle of Forel (H_2), the ansa lenticularis and the ansa peduncularis. This motor system of the corpus striatum is, therefore, a short internuncial system which arises in the corpus striatum and terminates in relation to important nuclei in the hypothalamic region, among which may be mentioned the corpus Luysii, the nucleus ruber, and the substantia nigra. Through these connections the corpus striatum exercises a controlling influence on automatic and associated movements through the medium of the extra-pyramidal motor tracts.

Diagnosis.—The diagnosis is not difficult. The early age of onset, the gradual progression, the Parkinsonian nature of the paralysis, rigidity and tremor produce a characteristic clinical picture. Distressing subjective disturbances—e.g., pain, numbness, sensations of heat and cold—so frequently met in the senile form, are absent.

In the early stage, there may be a certain resemblance to multiple sclerosis, on account of the early age, the violent and extensive tremor, speech disturbance, pseudo-nystagmus and spurious Babinski reflex. Careful attention to the true nature of the tremor and the elimination of spurious symptoms will, however, render the diagnosis clear. The same holds true for the primary spastic paraplegia for which, on account of the early age of onset, the affection has sometimes been mistaken.

There may also be a certain resemblance to the progressive lenticular degeneration, as both affections are often familial and both are types of an extra-pyramidal motor disorder with paralysis, rigidity and tremor of the Parkinson type. In Wilson's disease, however, the more rapid course, the general constitutional symptoms, fever, and emaciation, the mental disturbances, the hepatic cirrhosis, and especially the occurrence of choreiform and athetoid movements and muscular spasm, should be sufficient to render the diagnosis clear.

These spasmodic phenomena do not occur in progressive atrophy of the globus pallidus, and when present should be regarded as an indication of more expensive involvement of the corpus striatum.

The *prognosis* is absolutely unfavourable as regards cure, or even any considerable recession of symptoms. The affection, however, is but slowly progressive and is compatible with many years of life.

This, then, is the pathological type which I would isolate from the large Parkinsonian group or syndrome. The question of its frequency and occurrence in the later periods of life can only be settled by further pathological investigation. It, however, opens up a field for the future investigation of this subject and a more exact classification of the Parkinson syndrome.[1]

PART II.—THE CORPUS STRIATUM.

It is now my purpose to apply this pathological conception of the globus pallidus system to the larger question of the corpus striatum, in the hope that it may throw some light on an obscure and still mysterious field. I will not, however, review in detail the literature of this subject, as this field has already been thoroughly covered in many recent mono-

[1] It is not without interest to mention that two cases of paralysis agitans of later life, at present under investigation, also show definite atrophic changes in the large cells of the globus pallidus system. These evidences of cell atrophy are well marked in the large motor cells of the caudate nucleus and putamen, and consist of shrinking and diminution in size of the cell body; atrophic and hyaline appearance of the protoplasm; atrophy and fragmentation of the processes; excessive deposit of pigment and lipoid material; vacuolation of the protoplasm; contraction, deformity, and displacement of the nucleus. There is also a deposit of lipoid material in some of the pericellular spaces, and especially in the perivascular sheaths of the blood-vessels, which show evidences of marked arteriosclerosis. The evidences of atrophy in the large motor cells of the caudate nucleus and putamen are very striking, and there are reasons for the assumption that the giant cells of the neostriatum are the homologues of the Betz cells of the Rolandic area.

The small cells of the neostriatum are well preserved and there is slight increase of the glia nuclei, especially in the putamen. Atrophic changes in the large cells of the efferent pallidal system are, therefore, not confined to the juvenile type, but are also present in paralysis agitans of the presenile period.

graphs, especially those of Kinnier Wilson. I will emphasize merely certain facts, anatomical, pathological, and clinical, upon which I base two fundamental syndromes of the corpus striatum, viz., *the syndrome of the globus pallidus* and *the syndrome of the neostriatum*.

Chapter VI.—Anatomical Considerations.

The corpus striatum of mammals is divided by the passage of the anterior limb of the internal capsule into two parts, the nucleus lentiformis and the nucleus caudatus. The nucleus lentiformis is still further subdivided into an external segment, the putamen, and an internal which is termed the globus pallidus. These anatomical divisions are purely topographical, based upon the gross appearance of the cells and fibre systems which constitute the ganglion.

The putamen is identical in histological structure with the caudate nucleus, and with it forms the *neostriatum* of comparative anatomy, and while described as separate ganglia in man, they have the same origin and histological characteristics, the caudate being simply split off in the higher forms by the passage of capsular fibres.

The globus pallidus is described as having two segments, an inner and an outer, this grouping being produced by the fusion of nerve-fibres in the lateral and mesial medullary laminæ. This portion of the lenticular nucleus is much older phylogenetically than the neostriatum, and is termed the *paleostriatum*. It is a well-developed ganglionic structure, the *nucleus basalis*, as low in the animal scale as fishes. This nucleus gives rise to the *basal forebrain bundle*, and with the primary motor fasciculus of the spinal cord, and the fasciculus longitudinalis posticus, constitutes in these lower forms the essential central motor mechanism.

The neostriatum, on the other hand, makes its first appearance in reptiles, and is especially well developed in birds and mammals.

While the older anatomical divisions will probably always retain their vogue, it is well to emphasize the developmental differences between the globus pallidus, or paleostriatum, and the caudate nucleus and putamen, or neostriatum.

Not only is the globus pallidus much older phyletically, but also in its ontogenetic development. In the growth of the human fœtus this efferent fibre system develops before that of the neostriatum, and the early myelinization of the efferent globus pallidus fibres of the ansa lenticularis is a conspicuous anatomical feature of the fœtal brain.

Closely related to the globus pallidus in man is the *nucleus basalis of Meynert*. This is an aggregation of ganglion cells in the region of the ansa peduncularis, situated between the optic tract and the anterior commissure, beneath the globus pallidus. It is in all probability a derivative of the globus pallidus, and is composed of medium-sized cells, many of which contain pigment granules. Like the globus pallidus, this nucleus is primeval, and both in its phylogeny and ontogeny develops before the neostriatum.

The motor cells of the nucleus basalis and the large cells of the neostriatum I regard as physiologically related, and as part of the motor system of the globus pallidus mechanism. The motor cells of the globus pallidus mechanism do not, therefore, represent a sharply demarcated ganglion, but are widely distributed throughout the entire corpus striatum. They are most numerous in the globus pallidus proper, but are also found in inconsiderable numbers among the small ganglion cells of the caudate nucleus and the putamen. They are also present in the ganglion basale of Meynert beneath the globus pallidus, and also in small numbers among the fibres of the ansa radiations.

Cell Types of the Corpus Striatum (Neostriatum and Paleostriatum).

From the standpoint of pathological physiology a much greater importance is to be attached to the cellular types of this region than to the mere gross anatomical appearance and subdivisions.

The globus pallidus contains aggregations of fusiform, pyramidal, and large multipolar cells, which are histologically of the motor type. In addition to a characteristic arrangement of the Nissl granules, many of the cells contain a deposit of yellow pigment, and in many ways their appearance suggests the large pyramidal cells in the motor area of the cerebral cortex, or the multipolar cells of the anterior horns of the spinal cord. These cells are scattered throughout the globus pallidus, occurring often in groups and chains, and while varying somewhat in size conform essentially to a motor-cell type.

In contrast, the caudate nucleus and putamen are composed of two separate and distinct types of cells. The more numerous are the small pyramidal stellate or polygonal cells which give the characteristic histological picture of the neostriatum. Scattered among these smaller cells, however, are cells of larger size. These are large multipolar cells, containing Nissl granules and often a deposit of yellow pigment granules.

They resemble the large cells of the globus pallidus, and I regard them as identical not only in structure, but also in function.

This fundamental division of cell types in the corpus striatum has not escaped the notice of other observers. According to C. Vogt [46], the globus pallidus is an isomorphous ganglion, i.e., consisting of one cell type; while the neostriatum is allomorphous and composed of two distinct cell types. Starr [21], long since, recognized two varieties of cells in the corpus striatum: a large rectangular type, 70 microns in length and 10 to 15 microns in width, and a much smaller cell of triangular or stellate form.

The large ganglion cells of globus pallidus type possess long axis cylinder processes and correspond to Type I of Golgi's classification, while the smaller ganglion cells of the neostriatum have only short axis cylinder processes which terminate in the outer or inner segments of the globus pallidus. The longer axis cylinders of the globus pallidus cells course in the ansa system to the thalamic and hypothalamic regions. The small ganglion cells of the neostriatum, therefore, represent a short internuncial system which unites the caudate nucleus and putamen to the globus pallidus; the large ganglion cells of the globus pallidus mechanism constitute a short efferent projection system which unites the corpus striatum to important nuclei of the hypothalamic region.

Of special importance in the realm of cellular histology are the fundamental investigations of Malone [10]. Malone recognizes the possibility of distinguishing certain cell types in the various cellular groupings of the central nervous system, and believes it is possible, for example, to recognize the various members of the somatic motor chain by means of a fundamental type of cell structure. Furthermore, he believes that a definite type of cell structure corresponds to a definite cell function, and that similarity of type would indicate a similarity of function. As bearing on the question under discussion it is interesting to note that he regards the globus pallidus as the motor portion of the lenticular nucleus, and finds the optic thalamus quite free from cells of the motor type. In contrast, the hypothalamus contains numerous motor cells.

Among the various groupings which he identifies as motor by this histological method are: the anterior horn cells of the spinal cord and their homologues in the medulla and pons; the globus pallidus; those of the anterior central convolutions (cells of Betz); the large cells of the red nucleus giving rise to the rubrospinal tract; the motor cells of the anterior quadrigeminal body from which arises the tectospinal tract;

the cells of Deiters' nucleus whose axones constitute the vestibulospinal tract; the nucleus of the posterior commissure which sends some of its fibres to the posterior longitudinal bundle; the dentate and roof nuclei of the cerebellum; and certain cells in the formatio reticularis of the brain stem and hypothalamus.

In contradistinction to Jacobson [8], he does not consider the substantia nigra as motor, but states that in the oral portion of the black substance there are cells which extend laterally into the pes pedunculi which are definitely motor in structure. This small oro-lateral group he calls the *nucleus intra-pedunicularis*. The lenticular nucleus he divides into a mesial motor group, the globus pallidus, and a lateral sensory group, the putamen.

It would appear, therefore, from the studies of Malone that the corpus striatum contains a motor grouping of cells in its mesial portion, the globus pallidus. Furthermore, that it is possible to identify motor types of cells on the basis of their histological structure, and that similarity of cell type corresponds to similarity of cell function.

This view expressed by Malone is confirmed by my pathological studies of the globus pallidus system, which show that a selective systemic atrophy of the cells of motor type may occur in the corpus striatum with preservation of the smaller cells of sensory type of the neostriatum. For, in the progressive atrophy of the globus pallidus, not only are the cells of the globus pallidus proper involved, but the cells of similar histological type in the neostriatum and the nucleus basalis of Meynert are also affected. It is an example of abiotrophy, in which the neurones of a similar type and function have undergone a gradual decay.

Fibre systems of the corpus striatum.—The fibre systems of the corpus striatum, like the cellular systems, may be divided into two distinct groups; one group is composed of short internuncial fibres which take their origin from the small cells of the caudate nucleus and putamen, and terminate in the lateral and mesial segments of the globus pallidus. These fibres form the delicate medullary pencils which radiate in the neostriatum and give to this region a very characteristic histological picture. It is held by some authorities that these short internuncial fibres also pass in small numbers across the internal capsule in the striæ thalamici to the lateral margin of the thalamus. Wilson [22], however, has shown by a careful study with the Marchi method of the experimental lesions produced in monkeys, that these short internuncial fibres all terminate in the globus pallidus.

The second group of fibres constitute the ansa system, viz., the

ansa radiations, ansa lenticularis and ansa peduncularis. This system contains both efferent and afferent fibres; those which are efferent arise in the motor cells of the globus pallidus mechanism. The ansa system passes to the anterior and lateral portion of the thalamus and to the hypothalamic region. The exact termination of the efferent fibres has not been definitely determined; but some pass to the corpus subthalamicum, the nucleus ruber, and some probably to the substantia nigra. Below this level no degenerations are traced after lenticular lesions, so that the efferent ansa system is composed of short projection fibres which connect the corpus striatum with subsidiary centres in the hypothalamus and midbrain.

The connections of the corpus striatum. — Our knowledge of the various systems which enter into the formation of the corpus striatum is still very defective. Some important advances have been made in this direction in recent years, and the experimental investigations of Kinnier Wilson are especially deserving of mention.

The fibre systems of the corpus striatum are both efferent and afferent in character, and serve to unite this structure with the optic thalamus and the nuclei of the hypothalamic region. There are probably no connections between the corpus striatum and the cerebral cortex, nor do fibres pass from the striatum to the internal capsule. Fibres originating in the caudate nucleus and the putamen terminate in the globus pallidus, and according to Probst [17] and Grünstein [7], a few fibres traverse the internal capsule to terminate in the thalamus and hypothalamic region. In Wilson's experiment on monkeys, in which small electrolytic lesions were placed in the caudate nucleus and the putamen, with the stereotaxic instrument of Clarke and Horsley, the fine pencils of degeneration all terminated in the globus pallidus. No degenerations could be traced to the optic thalamus, the internal capsule, or to the cerebral cortex.

In similar experimental lesions of the globus pallidus, Wilson traced the secondary degenerations of the ansa fibres. These he divides into two groups, viz., those having a more transverse direction and of rather coarser texture which pass to and terminate in the ventral and lateral surface of the thalamus and the nucleus ruber; and those of finer quality and radial distribution which terminate in the corpus Luysii, nucleus ruber and the substantia nigra.

In man, therefore, the small cells of the caudate nucleus and putamen with their short axones terminate in the globus pallidus, a few perhaps crossing the internal capsule to the thalamus. The large cells of the

globus pallidus, with their longer axones, terminate in relation to important nuclei in the thalamic and hypothalamic regions, viz., the nucleus ruber, corpus Luysii and the substantia nigra.

There are in addition to these striofugal fibres also striopetal fibres, passing in the ansa from the thalamus, and I would repeat again the evidence is in favour of there being no direct connection with the cerebral cortex or with the pyramidal tracts. So what information we possess at the present time in regard to the fibre connections of the corpus striatum shows the close relationship of this structure to the thalamus and the hypothalamus and its freedom from direct cortical connections.

The results of modern anatomical investigations may therefore be summarized somewhat as follows: The corpus striatum is composed of two portions, the globus pallidus (paleostriatum) and the caudate nucleus and putamen (neostriatum). These two structures differ histologically and phylogenetically. The paleostriatum contains cells of a motor type with long axis cylinders which terminate in relation to nuclei of the thalamic and hypothalamic regions (striofugal fibres). The neostriatum is composed largely of smaller ganglion cells with short axis cylinders which terminate in the globus pallidus. This is a short internuncial system uniting the neostriatum and the paleostriatum. There are also found scattered through the neostriatum larger ganglion cells which resemble in structure the cells of globus pallidus type. These I regard, together with a more basal aggregation of motor cells (nucleus basalis of Meynert), as part of the efferent globus pallidus system.

The striatum has no direct connection with the cortex or the corticospinal system, its striofugal and striopetal systems of fibres uniting it with the thalamus and hypothalamic region.

The corpus striatum may, therefore, be regarded as an important motor-regulating centre, in the same sense as the optic thalamus is a sensory correlating mechanism.

Before the development of the corticospinal motor system, it was the important centre for the control and regulation of movements. With the development of the pyramidal tracts it lost some of its early importance, but, like the optic thalamus in the domain of sensation, it still plays in the realm of motion an important rôle in the control and regulation of automatic and associated movements.

Chapter VII.—The Corpus Striatum: Pathological Considerations.

For many years the corpus striatum, the optic thalamus and the regio hypothalamica have been regarded as having important relations to such involuntary movements as chorea, athetosis and tremor of the Parkinsonian type. There has been, however, no uniformity in the localization of lesions and their relation to these symptoms, and not infrequently a lesion has been found and the symptom, which should have been present, was absent. For example, a clinical picture resembling paralysis agitans has followed a gross lesion of the optic thalamus, as have also choreiform disturbances. On the other hand, chorea, athetosis and the Parkinsonian syndrome have been associated with lesions of the corpus striatum, and very evident lesions have been demonstrated in these various structures with no corresponding symptoms; all of which has tended to obscure the subject and confuse the issue.

In recent years many important pathological contributions, especially those with careful histological studies and serial sections, have served to clarify somewhat this obscure field, and there is, at the present time, quite a formidable array of pathological facts by which a somewhat clearer conception of the functions of this region may be obtained.

Paralysis agitans.—Jelgersma [82], in 1908, recorded certain curious pathological changes in the basal ganglia in both paralysis agitans and Huntington's chorea. In paralysis agitans he observed: a marked atrophy of the radiations of the nucleus lentiformis; a reduction in size of the ansa lenticularis and ansa peduncularis, of Forel's field H_1 and H_2; also an atrophy of the nucleus lateralis thalami, the corpus Luysii and the radiations of the substantia reticularis. He emphasized the fact that these atrophic changes were quite evident and unmistakable.

In Huntington's chorea he found atrophic changes in the head of the caudate nucleus which was reduced to one-third its usual size. There was also a marked proliferation of the glia cells.

Jelgersma's pathological studies were reported only in abstract, in the Proceedings of a Medical Society, and while very brief and incomplete, they served to direct attention to this region in these two diseases and opened the way to much subsequent pathological investigation.

Lewy [85], in the chapter on the Pathology of Paralysis Agitans, contributed to Lewandowsky's "Handbuch" in the discussion of

Jelgersma's findings, states that he has personally studied serial sections of five cases of Parkinson's disease, and asserts that an essential atrophy of the ansa lenticularis and the lenticular radiations does not occur. He admits, however, that there is repeatedly a diminution in the number of fibres in the ansa, which is especially marked in those cases in which there are well-developed vascular changes in the globus pallidus. He also notes the existence of atrophic changes in the nucleus basalis of Meynert, the nucleus lateralis of the thalamus and the nucleus paraventricularis thalami.

In a later contribution to the Pathological Anatomy of Paralysis Agitans, Lewy [84] states that the lesions are located as follows: viz., in the lenticular nucleus, the nucleus of the ansa peduncularis, and the sympathetic vagus nucleus of the medulla. In typical cases there is a great increase of the glia elements with degeneration of the ganglion cells, especially of the putamen, and less of the globus pallidus. Many of the ganglion cells show senile fibrillar changes. He closes with the statement that these pathological changes are essentially senile in character and a special explanation is wanting for the juvenile paralysis agitans cases.

Manschot [88], in his investigations of paralysis agitans, also found a diminution in the ganglion cells and fibres of the optic thalamus, especially of the nucleus lateralis, together with atrophic changes in the putamen and regio subthalamica.

Auer and McCough [77] have recently reported the pathological findings in two cases of paralysis agitans. In both, the corpus striatum contained numerous small areas of rarefaction, giving the tissue a moth-eaten appearance. Many of these spaces contained blood-vessels and were evidently enlarged perivascular spaces. This *état criblé* was most marked in the lenticular nucleus, but was also present in the optic thalamus, caudate nucleus, the internal and external capsule and the corpus subthalamicum. These observers also noted a reduction of the external medullary layer and the radial fibres of the globus pallidus, and in one of the cases there was marked degeneration of cells of the centrum medium of the thalamus and the corpus subthalamicum. They state that the cells of the corpus striatum did not stain well, which may have been due to the age of the material.

Löwy [86] has also recorded a case of paralysis agitans with areas of softening in the caudate and lenticular nuclei.

From these pathological studies of the basal ganglia in paralysis agitans, it would appear that the lesions, while definite, are by no means

sharply localized to any one structure. They are present in the optic thalamus as well as in the corpus striatum, and occasionally in the regio hypothalamica. Lewy, in particular, emphasizes the *senile character* of the histological changes.

Huntington's chorea.—Since Jelgersma's brief allusion to atrophic changes in the head of the caudate nucleus in Huntington's chorea, there have been a number of notable contributions bearing upon this question, viz., those of Alzheimer, Kleist, Marie and L'Hermitte and Dunlap.

Alzheimer [23] in a pathological study of three cases of Huntington's chorea found, in addition to cortical changes, advanced degeneration in the cells of both the caudate and lenticular nuclei; marked diminution in the number of ganglion cells, with a corresponding increase of the glia nuclei, without the formation of glia fibres. He also noticed the presence of lipoid material in the ganglion cells and glia cells and in the vessel walls. Evidences of cell degeneration were also noted in the regio subthalamica and to a lesser degree in the nuclei of the optic thalamus, the pons and the medulla.

Alzheimer [23] also carried out pathological investigations on the acute chorea of rheumatic and septic origin, and succeeded in demonstrating the presence of embolic foci, which were especially numerous in the corpus striatum and the regio subthalamica.

Kleist [38] and Kiesselbach [37], in a case of Huntington's chorea of fifteen years' duration, found widespread atrophic and degenerative changes. The caudate nucleus and the putamen were atrophic, with a reduction in the number of ganglion cells to one-quarter or one-fifth of the normal. The glia cells were considerably increased in number. Pathological changes were also noted in the optic thalamus, the globus pallidus, nucleus ruber and corpus subthalamicum. The frontal convolutions were atrophic as well.

A very thorough study of the pathological changes in chronic progressive chorea has been recently contributed by Marie and L'Hermitte [40], under the title of "La dégénération atrophique cortico-striée." Four cases of this disease were studied by modern histological methods and the chief lesions noted were of the cerebral cortex, more especially of the frontal and Rolandic regions, and of the caudate nucleus and putamen. While the globus pallidus was reduced in size, there were no evidences of degeneration or atrophy of the striothalamic fibres or ansa lenticularis. In certain of the cases degenerations were also noticed in the cerebellum and optic thalamus. They regard the affection as a form of chronic encephalitis resulting from chronic intoxication,

and would refer the intelligence defect of chronic chorea to the cortical changes and the *choreiform manifestations to the alterations in the corpus striatum.*

Dunlap,[1] in a large series of cases, in addition to other changes, has found uniformly an atrophy of the caudate nucleus and putamen, with degeneration and marked reduction in the number of ganglion cells and an increase of the glia nuclei.

There can therefore be little question as to the constancy of pathological changes in the corpus striatum in cases of Huntington's chorea, and the pronounced atrophy and diminution in the number of the cells of the caudate nucleus and the putamen (the neostriatum).

Athetosis.—The corpus striatum is the seat of pathological changes not only in paralysis agitans and Huntington's chorea, but also to a very marked degree in that rare affection known as idiopathic athetosis.

Athétose double.—Anton [24], as early as 1895, reported the pathological findings in a boy with progressive bilateral athetosis, who died at the age of 19. The outer segment (putamen) of the lenticular nucleus on both sides was the seat of extensive atrophy and degeneration. White medullated markings were noted traversing the atrophic area which was limited to the posterior $\frac{1}{3}$ of the putamen. The caudate nucleus was not involved. Anton reached the conclusion that chorea stands in relation to the grey matter of the putamen, and that the corpus striatum has an important co-ordinating and inhibitory effect on the central nervous system.

The pathology of *athétose double* has also been very thoroughly studied by Madame Cécile Vogt [46]. In four cases of this disease, which were carefully studied by the method of serial sections, the lesion was found limited to the caudate nucleus and the outer segment of the lenticular nucleus (putamen). There was an extensive destruction of the nerve cells of these structures, described as a *dystrophy* of the ganglion cells. A curious feature of the lesion was the presence of a thick network of medullated nerve fibres, traversing the atrophic areas of the caudate nucleus and the putamen, producing a marmorated appearance, which suggested the term *état marbré*.

This network of medullated nerve fibres she believes is produced by the transmutation of non-myelinated nerve fibres into medullated fibres and resembles the so-called *plaques fibro-myéliniques*, which are not infrequently encountered in the cerebral cortex.

[1] Reported at a meeting of the Section on Nervous and Mental Diseases of the New York Academy of Medicine, March 14, 1916.

All other portions of the central nervous system were normal, and it is especially noted that the internal capsule was free from atrophy or degeneration. The internal capsule gave the appearance of hypertrophy in some of the specimens, but this was merely the effect of the atrophy of the caudate nucleus and the putamen. The globus pallidus was somewhat atrophied in its dorsal portion; the ansa lenticularis, however, was not particularly affected, and no secondary degenerations were traceable to the optic thalamus.

On the basis of these clinical and anatomical investigations Madame Vogt reached certain important conclusions as to the functions of the corpus striatum. She believes that this structure has a certain regulating and inhibitory effect on the nervous system, and when the seat of a destructive lesion, as in *athétose double*, there is a loss of this inhibitory function and symptoms of athetosis supervene. This affection she regards as representing a pure syndrome of the corpus striatum, which consists of double athetosis with spastic contractures, and pseudobulbar palsy.

Fischer [29] has also contributed to the pathology of this question. The case was one of athetosis developing at about the fifteenth year. The condition was gradually progressive and terminated in tonic spasms; death occurred at the age of 21. A careful histological examination showed the following alterations in the corpus striatum: The whole lenticular nucleus was reduced in size. The putamen was smaller than normal and the globus pallidus was quite atrophic and the seat of a brownish discoloration. The caudate nucleus, however, was not affected. There was a considerable loss of the medullated nerve fibres of the globus pallidus and the ganglion cells were enlarged and rounded, the nucleus swollen and the nucleolus enlarged. Many of the cells contained granules and some were vacuolated and filled with brownish pigment. The globus pallidus was also rich in dark-staining glia cells, many of which contained pigment.

In summing up the pathological findings in this case, Fischer states that the destructive process was limited to the globus pallidus, both fibres and cells, and regards it as a special clinical type of progressive double athetosis. No mention is made of any examination of the liver in this case, and as the clinical notes are meagre an exact classification is rather difficult. The pathological findings, however, awaken the suspicion of the progressive lenticular degeneration and the clinical notes are very suggestive of a certain type of that disease, viz., the tetanoid chorea of Gowers. It may, however, represent a pathological type which stands midway between Wilson's disease and the *état marbré* of Vogt.

Progressive lenticular degeneration.—The most important and fundamental contribution to the symptomatology and pathology of the corpus striatum is that of Kinnier Wilson [106], the progressive lenticular degeneration.

The disease described by Wilson is characterized by symmetrical bilateral degeneration of the lenticular nucleus, chiefly of the putamen, less of the globus pallidus. The caudate nucleus is often atrophic, but never in the same degree. The fibres of the internal capsule are intact and the thalamus is normal, save for the loss of striothalamic fibres and a thinning of the lamina medullaris externa.

The degree of the degeneration varies in different cases from a discoloration and porosity of the nucleus lentiformis to marked atrophy or disintegration of the affected nucleus. In extreme cases there is complete degeneration and cavity formation. Microscopically, there is marked proliferation of the glia with degenerative changes, but without evidences of vascular occlusions or inflammatory lesions.

These degenerative changes in the corpus striatum are always associated with a lobular cirrhosis of the liver.

The essential symptomatology of this group of cases is characterized by progressive rigidity and tremor of the paralysis agitans type, associated with a tendency to tonic or clonic spasms. In some of the cases a well-marked tendency to spontaneous movement of a choreiform or athetoid character was observed. This latter peculiarity of the progressive lenticular degeneration I would particularly emphasize, and is shown by the titles originally applied to the disease by so skilful a clinical observer as Gowers [99], viz., the tetanoid chorea.

This tendency to involuntary spasm and athethoid movements is in marked contrast to the other truly Parkinsonian features of the disease, and will be discussed more in detail in the chapter on the Syndromes of the Corpus Striatum.

Chapter VIII.—The Functions and Syndromes of the Corpus Striatum.

In the chapter on the anatomy of the corpus striatum special emphasis was laid on the early appearance of this structure in the course of phylogenetic development, resembling in this respect the optic thalamus, with which it is intimately associated by both afferent and efferent association systems.

In the lower forms of life before the development of the cerebral

cortex, when the pallium is represented by a mere rudimentary membrane, the optic thalamus and corpus striatum are important correlating and regulating centres. Together they constitute the essential sensori-motor mechanism for the reception of afferent stimuli and the regulation of motor activities.

These structures are concerned with more primitive forms of sensation and motion than is the cerebral cortex, but that their functions still persist and are of considerable importance in man is shown by the effects of injury or disease.

In the lower forms of fishes the *nucleus basalis*, which is the forerunner of the globus pallidus, is a very conspicuous feature. Indeed, the large-cell nucleus of the globus pallidus or paleostriatum is a conspicuous ganglionic structure throughout the animal series. In these lower forms, this nucleus is closely related to an important efferent tract, known as the basal forebrain bundle (*Basales Vorderhirn Bündel* of Edinger [6]), which unites the nucleus basalis with various cell groupings in the 'tween and mid brain.

The homologue of this system in man is the corpus striatum (paleostriatum and neostriatum) and its thalamic and hypothalamic radiations. A structure of this character which appears so early in the animal series, and is so persistent, must subserve an important function in the central nervous system of man. I believe that the atrophic changes in the pallidal system of juvenile paralysis agitans throw an important light on the functions of this mechanism.

Anton, a number of years ago, pointed out the relationship of chorea and athetosis to lesions of the outer segment of the lenticular nucleus (putamen) and reached the conclusion that the striate body plays an important rôle in the regulation of the motor function of the nervous system. The basal ganglia he regarded as a sensori-motor organ possessing important co-ordinating and inhibitory functions. He ascribed to the corpus striatum a predominantly motor or efferent function and to the thalamus a sensory or afferent function and emphasized the close connection of these two large ganglia by association tracts.

Subsequently, in 1911 and 1912, Madame Vogt, in an elaborate pathological study of the same group of cases (double athetosis) reached somewhat similar conclusions and formulated a syndrome of the corpus striatum which had as its characteristic features double athetosis, spastic diplegia and dysarthria. Madame Vogt also emphasized the inhibitory function of the corpus striatum and its relation to the motor disturbances of chorea and athetosis.

Like Anton, Madame Vogt regarded the corpus striatum as a sensori-motor organ with certain co-ordinating and inhibitory functions, and, when the seat of a destructive lesion, there followed choreo-athetoid movements and spastic contractures, without evidences of pyramidal tract involvement.

The importance of these observations of Anton and Vogt in relation to the functions of the corpus striatum is obvious. They were dealing with a well-recognized clinical type, of definite symptomatology, in which a progressive circumscribed lesion was demonstrable, limited to the caudate nucleus and putamen—in other words, the neostriatum and its fibre systems. It was a circumscribed pathological lesion in man, having all the importance and significance of an experimental lesion and must be accepted as proving that destruction of the neostriatum is followed by choreo-athetoid movements and a certain amount of rigidity of the musculature. In this affection, according to the extent and severity of the lesion, such symptoms as chorea, athetosis, muscular rigidity, mobile spasm and dysarthria appeared in various combinations.

I would particularly emphasize the combination of choreo-athetosis and muscular rigidity in this group of cases, and its bearing on the two fundamental syndromes of the corpus striatum which will be described later, viz., chorea and paralysis agitans.

This relationship of the lenticular nucleus, and more especially of the putamen, is shown by many other clinico-pathological observations in which athetosis has been associated with circumscribed non-progressive lesions in this region.

In the chapter on the pathology of the corpus striatum, I have already referred to the pathological findings in hereditary chorea and the widespread cellular degeneration in the neostriatum (caudate nucleus and the putamen) which occur in this disease; and while there may be other portions of the central nervous system, viz., the optic thalamus, cerebral cortex, and superior cerebellar peduncles, in which a lesion may produce chorea or athetosis, there can be no question as to the great importance of the neostriatum in this relation.

As is well known, chorea and athetosis form a part of the so-called thalamic syndrome and many observations would indicate a relationship of these symptoms to the optic thalamus, more especially its lateral nucleus. In the classical observation of Edinger [28], choreo-athetosis supervened several months after the onset of the initial symptoms; the lesion in this case had, however, involved not only the thalamus,

but a small portion of the putamen as well. The choreo-athetosis in certain cases of the thalamic syndrome may have this origin; in others, the lesions of the lateral nucleus of the thalamus or of the afferent portion of the striothalamic radiations may secondarily induce these symptoms through their connections with the cells of the neostriatum.

When the superior cerebellar peduncles are involved chorea may be produced in a similar manner through the direct connections with the optic thalamus (cerebello-rubro-thalamic fibres), and the same mechanism may also explain chorea after cortical lesions in early life, irritation taking place through the corticothalamic fibres.

In any event, we must recognize the neostriatum as an essential factor in the control and regulation of movements, and when this is destroyed there result the phenomena of chorea or athetosis, and it is still an open question as to just what rôle the cortex, cerebellum and thalamus play in the production of this particular group of symptoms.

The most important contribution to the symptomatology of the corpus striatum is that of Wilson, founded on the progressive lenticular degeneration. This group of cases presented the symptomatology of paralysis agitans, i.e., rigidity and tremor, with the addition, however, of clonic and tonic spasms, a tendency which is quite foreign to the symptomatology of Parkinson's disease. There was not only a tendency to clonic and tonic spasms, but in certain of the cases a quite definite development of athetoid movements, as in the case of Gowers. One has only to recall the original title of Gowers's early description of the disease, the "tetanoid chorea," to realize the occasional prominence of the involuntary spasmodic tendency in this group of cases.

So here again there occur chorea, athetosis and mobile spasms in a lesion limited to the corpus striatum. In this group of cases, however, the lesion is not limited to the neostriatum, but involves as well the globus pallidus. There is, therefore, a mixed symptomatology, viz., paralysis agitans, plus an involuntary spasmodic or choreiform tendency. This is produced by a mixed lesion of the corpus striatum, which involves both its cortex, the neostriatum, and its motor centre, the globus pallidus.

The essential symptomatology of the corpus striatum consists, therefore, of chorea, athetosis, mobile spasm, rigidity and tremor of the paralysis agitans type.

I shall now endeavour to explain and reconcile these various symptoms and syndromes on the basis of my investigations of the globus pallidus system.

Chapter IX.—The Syndrome of the Globus Pallidus.

In juvenile paralysis agitans the essential lesion is an atrophy and disappearance of the large motor cells of the efferent pallidal system. This affection I would therefore regard as a pure system disease, analogous to primary lateral sclerosis, and as such an ideal lesion from which to form a conception of the functions of the globus pallidus. Lesions of another character, vascular, inflammatory, or neoplastic, would naturally involve other systems, thus complicating the clinical picture and causing confusion. This objection is of course eliminated in a primary system disease.

The cellular atrophy in my case was limited to the large motor cells of the corpus striatum and was present in the globus pallidus, the basal nucleus of Meynert and especially the neostriatum (caudate nucleus and putamen). Cells of similar character which are normally present in small numbers in the ansa radiations were also atrophic. This motor mechanism of the globus pallidus is therefore not sharply circumscribed, but radiates into both the neostriatum and the sublenticular region, an important consideration for the explanation of the varied symptomatology of this region.

Primary atrophy of the efferent pallidal system produces the pure clinical picture of paralysis agitans, viz., paralysis, rigidity and tremor of the Parkinson type, and these motor disturbances may be regarded as the expression of the loss of this motor mechanism. In short, *the syndrome of the globus pallidus is a paralysis, rigidity and tremor of the Parkinson type.*

In recent years there have appeared many important contributions to the motor disturbances of paralysis agitans, notably those of Zingerle [96] and Förster [79], which appear to show conclusively that the hypertonicity of the muscles in this affection is of central origin, resembling in many of its features the tonicity of spastic paralysis and yet presenting certain differences. One important distinction is to be found in the nature of the hypertonus. The tonicity of spastic paralysis is more under the control of peripheral or reflex stimuli, while the rigidity of Parkinson's disease is of a more central character. For example, spasticity diminishes after section of the posterior roots and in tabes dorsalis, while the rigidity of paralysis agitans is not affected.

Another peculiarity is the nature of the motor disturbance itself. This is characterized by a slowness of movement, which in part is due

to the rigidity; also a certain loss of the power of initiating movements, together with a grave disturbance of the association mechanism. This loss of the association of movement is shown in a variety of ways: on rising from a chair, in the act of sitting down and in walking. One has only to recall the stiff posture of the arms in walking to realize that the association mechanism is gravely affected. Contrast the stiff, motionless arms of Parkinson's disease with the jerky, associated movements of the paralysed arm in the hemiplegic, and it is apparent that in one the mechanism for the association of movement is intact and in the other it is lost or seriously affected. Observe a patient of paralysis agitans rising from a chair, with every indication of an extreme effort, and yet making no attempt to use the arms. Such an astounding lack of co-operation on the part of the upper extremities would be very difficult to explain save as a grave disorder of the mechanism for the association of movements.

If a case of advanced paralysis agitans is suddenly pushed over, the equilibrium is lost, but without the usual compensatory efforts on the part of the automatic and association motor mechanism. This is in marked contrast to the falling of a hemiplegic whose association mechanism is intact.

A patient with paralysis agitans is therefore dependent upon his cortical motor mechanism in performing acts which normally are largely under the control of an important automatic and association centre in the corpus striatum. The loss of this mechanism explains the difficulty in initiating movements, the conspicuous inertia, and the peculiar disturbances of the association of movements in habitual and more or less automatic acts. It also affords an explanation of the peculiar propulsion disturbances of gait, viz., a man with rigidity of the muscles attempting to walk under the guidance of his cortical and cerebellar mechanism, without the safeguard of the corpus striatum which normally regulates such acts. That this is not produced by weakness and hypertonicity of the muscles is shown by the absence of a propulsive tendency in ordinary spastic paralysis. Here, the automatic and association mechanism being intact, the difficulty in walking is one of weakness and hypertonicity.

Spastic paralysis may therefore be regarded as a defect of the pyramidal tract system with loss of cortical movements, and paralysis agitans as a defect of the globus pallidus mechanism with loss of the control of automatic and associated movements. The slowness of movement, the inertia, and the deficiency of motor initiative in this

disease I would also refer to the loss of this mechanism, as these patients are almost wholly dependent upon their cerebral cortex for acts and movements which are largely involuntary and automatic. The activities of the paralysed side in the ordinary spastic hemiplegia are in large part due to the preservation of this automatic and association motor mechanism. The grave disturbances of gait in paralysis agitans, viz., the propulsion, retropulsion, and lateropulsion, occur because this mechanism is at fault.

We have then two important motor centres in the central nervous system—the one *cortical* in the Rolandic area formed by the cells of Betz and the pyramidal tracts; the other *pallidal*, represented by the motor cells of the globus pallidus mechanism and its efferent fibre system in the striothalamic and hypothalamic radiations. The corticospinal system stands in relation to the peripheral motor neurones of the brain-stem and spinal cord—the globus pallidus system with important centres in the thalamic and hypothalamic region—notably the nucleus ruber, corpus Luysii and the locus niger. Through these the corpus striatum exerts a controlling influence upon the descending tracts of the extra-pyramidal motor system and the various units of the segmental nervous system. That such a mechanism exists is shown conclusively by the experimental studies of Starlinger [20], Munk [15] and Rothmann [18]; section of the pyramidal decussation and extirpation of the motor cortex producing only transient weakness of the extremities in dogs and monkeys.

In addition to the function of innervation, both of these higher motor centres, *cortical* and *pallidal*, exercise a controlling or inhibitory influence on peripheral muscle tonus, and when this inhibitory centre is destroyed the peripheral tonus mechanism is uncontrolled, and there results the spasticity of pyramidal tract disease or the rigidity of paralysis agitans.

The rhythmical tremor of the Parkinson type is one of the characteristic symptoms resulting from loss of the globus pallidus mechanism. The factors underlying the causation of this tremor are not definitely known. It has been suggested by some observers that it is a part of and dependent upon the degree of muscular rigidity, and to use the words of Hughlings Jackson: "Tremor is rigidity spread thin, and rigidity is tremor run together." It may also be recalled that in spastic palsies there is a tendency to tremor in the various clonic phenomena so characteristic of the spastic condition.

There is however a large group of cases of paralysis agitans which run their course practically without tremor, and in these cases the rigidity, so

far as can be determined, does not vary in character or degree from those cases which are associated with tremor. The occurrence of typical tremor is also rarely observed without a trace of rigidity (tremor type of paralysis agitans), all of which speaks rather against the theory of the dependence of tremor upon the degree of muscle tonus.

I would therefore suggest the possibility of an *inhibitory tremor centre* in the hypothalamic region which is under the control of the globus pallidus mechanism, and when this is diseased the centre is released from control and the tremor disturbance results. In this way one could explain satisfactorily those cases of paralysis agitans with rigidity or tremor alone.

In any event our knowledge of the origin of tremors is very slight, and it is not without interest to speculate on this symptom in its relation to the globus pallidus mechanism.

Chapter X.—The Syndrome of the Neostriatum.

According to the morphologists, the neostriatum (caudate nucleus and putamen) makes its first appearance in reptiles and then gradually increases in size as the animal scale is ascended. In birds this structure has already reached a very considerable size. It surmounts the globus pallidus as a sort of cap or cortex, and is very rich in ganglion cells. These are of two types: a small-cell type and a large-cell type. The smaller cells are polygonal or triangular in form, and these predominate; the larger cells resemble in their histological characteristics the globus pallidus cell type and are scattered in small numbers through both the caudate nucleus and putamen.

In discussing the progressive atrophy of the globus pallidus emphasis was placed upon the atrophy and disappearance of the large-cell type of the neostriatum as part of the pathology of that condition. I would now speak of the probable function of these smaller cells of the neostriatum.

If one reviews the pathological findings in the more recent studies of Huntington's chorea, it will be noted that atrophy of the caudate nucleus and putamen is a conspicuous feature. These structures show a considerable reduction in size, with widespread atrophy of the ganglion cells and a corresponding increase of the glia nuclei. In addition to these changes in the neostriatum atrophic changes are also present in the cerebral cortex, especially in the frontal and Rolandic areas. The two chief symptoms of the hereditary chorea, viz., the progressive

dementia and chorea, are in all probability dependent upon these pathological alterations—the mental impairment due to the cortical changes and the motor disturbances to the degeneration of the neostriatum. It is of course possible that chorea and choreiform disturbances may be dependent, in part at least, upon the cortical degenerations in this disease. There is, however, so much pathological evidence indicating the close relationship of the neostriatum to choreiform manifestations that one can hardly deny this relationship in Huntington's chorea, where the atrophy of the neostriatum is so marked a pathological feature.

As the lesion of juvenile paralysis agitans is limited to the large-cell system of the corpus striatum, it seemed to me of interest to study the corpus striatum of Huntington's chorea from this point of view.

Through the courtesy of Dr. Dunlap, of the New York Psychiatric Institute, I was enabled to study sections of the corpus striatum from five of his large series of cases of Huntington's chorea. In all of these cases the large cells of the globus pallidus type throughout the corpus striatum were well preserved amid the wholesale loss and destruction of the smaller type of ganglion cells of the neostriatum. There was a very considerable reduction in the size of the entire corpus striatum, with atrophy of the short internuncial fibres of the caudate and putamen, which terminate in the globus pallidus; but especially remarkable was the widespread atrophy of the small ganglion cells of the neostriatum. The other striking feature of the histological picture was the preservation of the large cells of the globus pallidus type in both the lenticular and caudate nuclei. Preservation of the large cells of the globus pallidus type in the corpus striatum of Huntington's chorea was also noted by Kiesselbach [37].

I would therefore suggest the relationship of the smaller type of ganglion cells of the neostriatum to the symptom-chorea, and when this cellular mechanism is destroyed there result the motor phenomena of Huntington's chorea.

This small-cell type of the neostriatum I would regard as subserving a cortical function to the neostriatum, acting in an inhibitory and co-ordinating capacity to the globus pallidus mechanism, with which it is in close association through the short internuncial system which unites the neostriatum to the paleostriatum.

As I conceive the corpus striatum, it is composed of two separate and distinct cellular systems; a pallidal or large-cell type which has a motor function, and a neostriatal or small-cell type which is inhibitory

or co-ordinating. Both of these cellular types may be the seat of selective or system degenerations. Atrophy of the motor system produces paralysis agitans; atrophy of the inhibitory and co-ordinating system produces choreiform movements of the Huntington type. The one is a motor centre, the homologue of the motor cells of the Rolandic area; the other is a controlling and association mechanism, the homologue of the other cellular layers of the cerebral cortex. As the corpus striatum has no direct connections with the cerebral cortex, its two systems of cells must be controlled through the medium of the optic thalamus, with which it is closely associated by the *afferent* fibres of strio-thalamic and strio-hypothalamic radiations.

Through these connections the corpus striatum would receive impressions from the general sensory system, the cerebellum and the cerebral cortex (corticothalamic fibres), all of which would be essential for the proper control and regulation of an automatic and association motor mechanism.

This conception of the functions of the corpus striatum is not at variance with the other syndromes which have been ascribed to this region. Indeed, it may be said to reconcile them. The syndrome of the corpus striatum, enunciated by Madame Vogt in 1911 on the basis of a destructive lesion of the neostriatum, in the *athétose double* is characterized by choreic and athetoid movements, spastic diplegia (without pyramidal tract involvement) and dysarthria.

In this syndrome both types of cells in the neostriatum, the small inhibitory and the large motor, are the seat of a destructive lesion, and accordingly there is rigidity plus chorea, which would produce the athetoid movements and mobile spasms so characteristic of this disease. In other words, I should regard the athetosis in this group of cases simply as a choreiform tendency plus a moderate degree of rigidity which would ensue from involvement of the large globus pallidus cells in the neostriatum.

The relationship of chorea and athetosis is still a matter of dispute. Most observers regard chorea and athetosis as closely related, the one passing by gradual transition into the other, so that no sharp line of demarcation can be drawn between them. Such terms as choreo-athetosis seem to show the difficulties encountered by most observers in the description of these types of involuntary movements. My explanation of the origin of athetosis, that it is chorea plus rigidity from involvement of both inhibitory and motor cells of the neostriatum, should throw some light on this question. Lewandowsky especially

denies any relationship between chorea and athetosis, and regards them as quite separate and distinct motor manifestations.

When I say that chorea and athetosis are dependent upon the degree of involvement of these two systems of the neostriatum, I do not deny the possibility of chorea and athetoid movements occurring after lesions elsewhere in the central nervous system, e.g., in the optic thalamus, the cerebellar peduncles, or the cerebral cortex. That there is, however, a chorea of striatal origin cannot be gainsaid, and when this assumes an athetoid character, according to my conception, it would indicate a partial involvement of the pallidal mechanism as well.

The other syndrome of the corpus striatum is that enunciated by Wilson on the basis of the progressive lenticular degeneration. This is a massive destructive lesion limited to the lenticular and caudate nuclei. Here the entire globus pallidus and the neostriatum are jointly involved, the resulting symptomatology of which is rigidity and tremor of the Parkinson type with clonic and tonic spasms, and in some of the cases even involuntary movements of a choreiform and athetoid nature (Gowers's tetanoid chorea).

According to my conception of the functions of this organ, the rigidity and tremor of the paralysis agitans type are dependent upon involvement of the globus pallidus mechanism, while the involuntary motor disturbances, viz., the clonic and tonic spasms, the choreo-athetoid movements, are occasioned by the release of the cortical inhibitory mechanism of the neostriatum. The variations in the symptomatology in this group of cases are therefore dependent upon the relative degree of involvement of these two systems. If the neostriatum were earliest and chiefly affected in Wilson's disease, the choreo-athetoid element of the symptomatology would be more in evidence, as in Gowers's type; whereas if the globus pallidus mechanism were chiefly affected the dominant symptoms would be those of paralysis agitans as in Wilson's cases.

Résumé.

I would therefore regard the corpus striatum as a higher co-ordinating motor centre which predominates over the realm of automatic and associated movements. It stands in close relationship with the important correlating sensory station, the optic thalamus, and through this structure with the peripheral sensory mechanism, the cerebellum and the cerebral cortex.

In the lower forms of life, before the appearance of the pyramidal tracts and the cerebral cortex, it is the chief co-ordinating motor mechanism, and through its connections with important nuclei of the hypothalamic region controls and directs the activities of the primitive motor system. In its more primitive form this mechanism is represented by the nucleus basalis, the basal forebrain bundle, and the primary somatic motor fasciculus of the spinal cord.

In man, this motor mechanism still persists and subserves important functions in the control and regulation of automatic and associated movements. Like the other lower motor centres it is probably under the control of the cerebral cortex, but also having important independent functions, and when destroyed there is a corresponding disturbance of motor function. This disturbance of motor function may manifest itself in various ways, depending upon the localization and degree of involvement of the two essential fibre systems of the corpus striatum.

When the large cells of the pallidal system are destroyed there results the paralysis agitans syndrome.

If the small inhibitory and co-ordinating cells of the neostriatum are affected, there is chorea of the Huntington type. Limited or massive involvement of these two systems produces the syndromes formulated by Madame Vogt and Kinnier Wilson.

The nervous system of man may therefore be said to present the possibility of three fundamental types of palsy :—

(1) A spastic paralysis of corticospinal origin, from destruction of the central motor neurones ;

(2) An atrophic paralysis of peripheral origin, from destruction of the peripheral motor neurones ; and

(3) A paralysis agitans of pallidal origin from involvement of the motor neurones of the globus pallidus mechanism.

All three of these systems are essential for the proper functions of normal motility. If there is loss of the pyramidal tract system alone, there is preserved a considerable degree of power of automatic and associated movement, which, however, is sadly limited by the hypertonicity of the musculature. If there is loss of the globus pallidus system alone, there is present a considerable degree of movement of cortical origin which in its turn is limited by the hypertonicity of paralysis agitans. Loss of the peripheral motor system, the final common path of Sherrington, abolishes all movement—cortical, pallidal, or reflex.

The peripheral system is the oldest of the motor tracts and is

intimately associated with the muscle fibre, muscle tonus, and the various reflex activities of the spinal mechanism. The globus pallidus then appears very low in the animal scale and is to be regarded as the co-ordinating and regulating mechanism of the peripheral system of neurones, presiding over the automatic and associated movements of these lower forms of animal life ("*Gemeinschafts-Bewegungen*"). With the advent of the pyramidal tract system in the higher forms there appears a finer differentiation of motion which is the power of isolated synergic movements ("*Isolierte Bewegungen*"). In man, these various motor functions are to a large extent interdependent, and a destruction of any one impairs the function of those remaining.

In this way only may be explained the severe disturbances of motility resulting from loss of either of the higher motor centres, cortical or pallidal.

Chapter XI.—Conclusions.

As a result of this clinical and pathological study the following conclusions are suggested :—

Clinical.—The juvenile form of paralysis agitans is a pure system disease characterized by a progressive atrophy of the efferent motor neurones of the globus pallidus mechanism. This affection may be distinguished from other types of paralysis agitans as *progressive atrophy of the globus pallidus*, or *primary atrophy of the pallidal system*.

It is a bilateral organic disease of the central nervous system beginning in the earlier decades of life, often familial, and is characterized by progressive rigidity and tremor of the paralysis agitans type and paralysis of certain automatic and associated movements.

Some cases of paralysis agitans beginning in later life probably also belong to this pathological type and are susceptible of differentiation from the senile, arteriosclerotic and other pathological forms of this affection.

The paralysis agitans group, properly speaking, is a syndrome, having a more or less common symptomatology as spastic paralysis, but including a variety of distinct pathological conditions, e.g., system degeneration (abiotrophy), senile degeneration and atrophy, vascular and perivascular lesions, toxic degenerations, tumours, lues, inflammations, &c.

Pathological.—The pathological changes in progressive atrophy of

the globus pallidus consist of atrophy and diminution in number of the motor cells of the globus pallidus mechanism, i.e., of the globus pallidus proper, the ganglion basale of Meynert and especially the cells of similar type scattered through the caudate nucleus and the putamen (neostriatum). These evidences of cellular atrophy are especially well marked in the large cells of the neostriatum. In addition to the atrophy and disappearance of ganglion cells there is a corresponding increase of the glia nuclei and a thinning of the fibres of the ansa system—striohypothalamic radiations. The small ganglion cells of the neostriatum are intact and the pyramidal tracts show no signs of atrophy or degeneration. The cells of the nucleus ruber, corpus Luysii and substantia nigra are normal, so that the pathological changes represent a primary system degeneration limited to the efferent motor neurones of the globus pallidus mechanism.

In Huntington's chorea the cells of globus pallidus type are preserved, both in the globus pallidus (paleostriatum) and in the caudate nucleus and putamen (neostriatum), where there is widespread degeneration of the smaller ganglion cells.

The smaller ganglion cells of the neostriatum may therefore be regarded as co-ordinating and inhibitory in character, and when destroyed the phenomena of chorea result.

Physiological.—The corpus striatum is the great infracortical centre for the control and regulation of automatic and associated movements. It is composed of two cellular systems, viz., the small ganglion cells of the caudate nucleus and putamen (neostriatal) and the large motor cells of the globus pallidus mechanism (pallidal). The function of the neostriatal cells is inhibitory and co-ordinating; that of the pallidal cells is motor.

Loss of the small-cell inhibitory system is followed by chorea; loss of the large-cell motor system by the paralysis agitans syndrome, viz., rigidity, tremor, and disturbances of automatic and associated movements.

A destructive lesion involving both types of cells in the caudate nucleus and putamen (the *état marbré*) produces the *Vogt syndrome* of the corpus striatum, viz., spastic diplegia with athetosis, rhythmic oscillations and pseudobulbar palsy. A massive lesion of the whole corpus striatum as in progressive lenticular degeneration produces the *Wilson syndrome*, viz., tremor and rigidity of the paralysis agitans type, together with tonic and clonic spasms and occasionally choreic and athetoid movements (Gowers's tetanoid chorea).

The Vogt syndrome and Wilson's syndrome therefore represent different degrees of involvement of these two cellular systems. The occurrence of muscular rigidity, rhythmical tremor, chorea, athetosis, tonic, clonic and mobile spasms will depend upon the distribution and extent of the lesion in the corpus striatum and the relative degree of involvement of these two cellular systems.

Athetosis, therefore, is simply a combination of chorea and rigidity from simultaneous destruction of the smaller (inhibitory) and larger (motor) cell types of the neostriatum.

The globus pallidus mechanism is the motor nucleus of the striate body and through its connections with important centres in the hypothalamic region—viz., the nucleus ruber, corpus subthalamicum and substantia nigra—exercises a controlling influence upon the segmental nervous system through the medium of the extra-pyramidal motor tracts. The corpus striatum has also close relations with the cerebral cortex, the cerebellum, and the peripheral sensory mechanism, through its connections with the great sensory correlating station, the optic thalamus.

The cells of the globus pallidus type, therefore, occupy the same position in the extra-pyramidal motor system as do the motor cells of the cerebral cortex in the corticospinal system; the globus pallidus mechanism controlling automatic and associated movements, whereas the higher cortical centres are concerned with isolated synergic movements.

Both of these mechanisms, in addition to the function of motor innervation, have also a controlling or inhibitory effect upon muscle tonus, so that a destructive lesion of either has as a result paralysis of a special type plus an increase of muscular tonus. A lesion of the pyramidal tract system is followed by the phenomena of spastic paralysis; a lesion of the pallidal system by the phenomena of paralysis agitans.

Three fundamental types of motor palsy may therefore be recognized; two are central and one is peripheral:—

(1) A spastic paralysis of cortical origin—from involvement of the first or central motor neurones;

(2) A paralysis agitans of pallidal origin—from involvement of the motor neurones of the globus pallidus mechanism;

(3) An atrophic paralysis of peripheral origin—from involvement of the second or peripheral motor neurones.

* * * * *

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